Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

VOL. 54 APRIL 1961 NO. 4

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APRIL 1961

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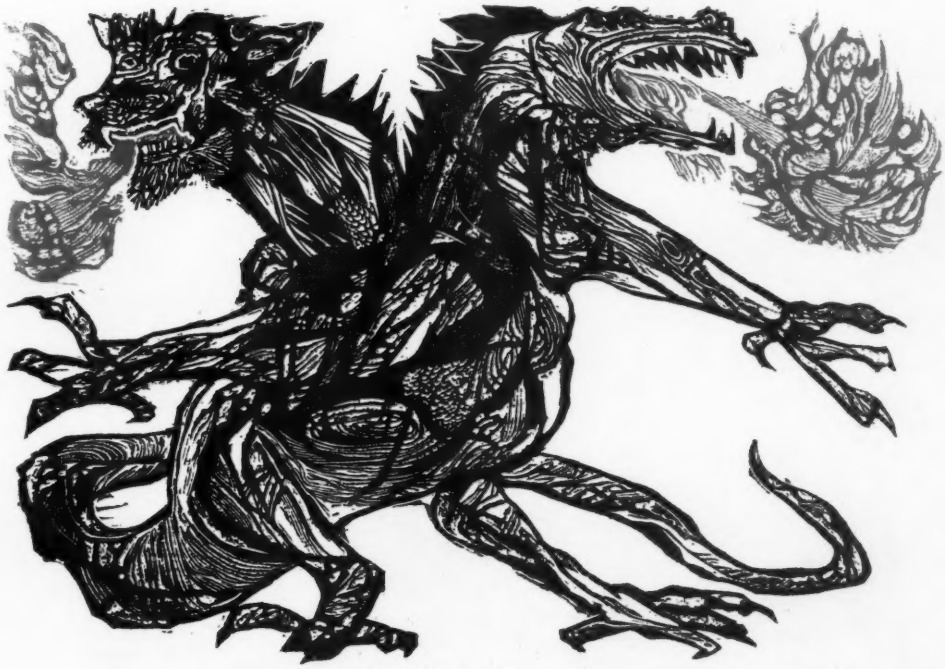

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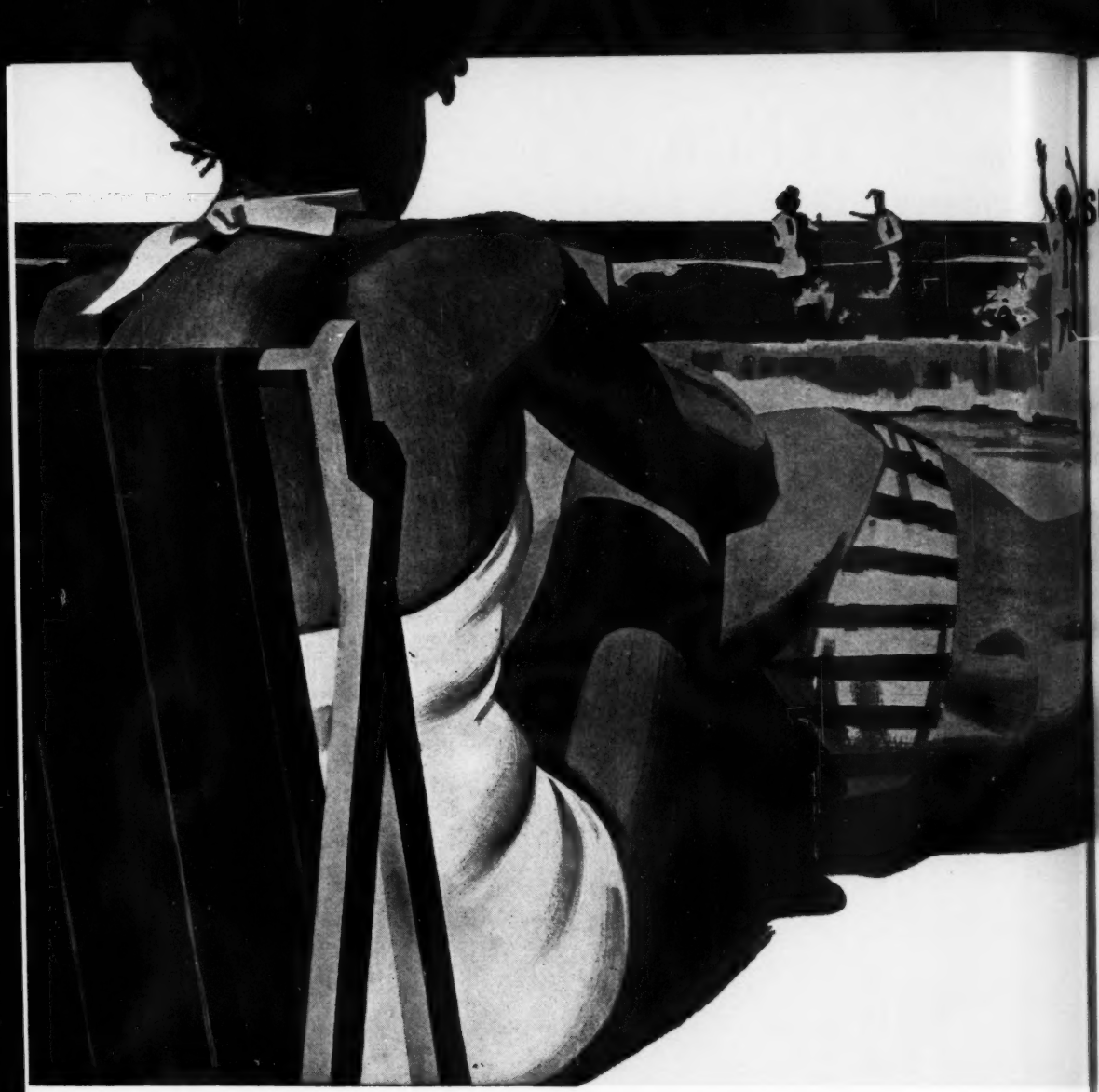

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PACKAGE INFORMATION: ELASE is supplied as an ointment in 30-Gm. and 10-Gm. tubes. Disposable vaginal applicators (V-Applicators) for application of ointment are available separately in packages of 6. ELASE is also supplied as lyophilized powder in rubber-diaphragm-capped vials. To be maximally effective, the solution must be freshly reconstituted with isotonic sodium chloride just prior to topical use. Within six hours after preparation, half of its potency is lost at room temperature.

FEB. 1961 (P-546)

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Elase

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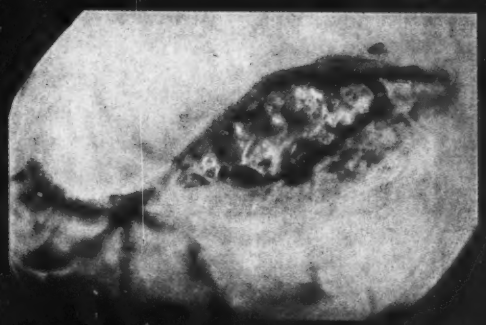
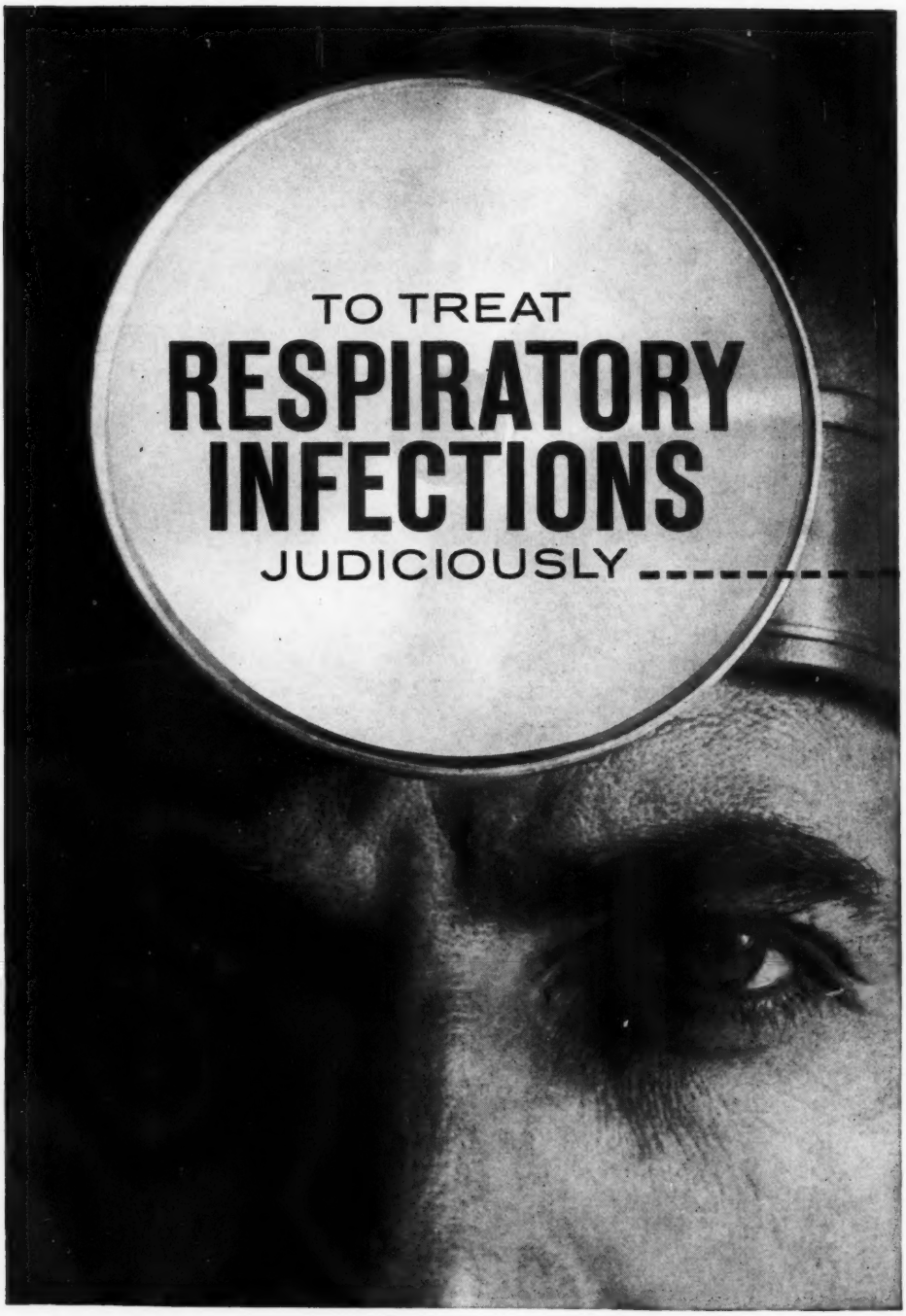
Draining wound four weeks postoperatively and prior to enzymatic therapy. Infective organisms identified were Pseudomonas and coagulase-positive staphylococci.



Eight days later. Solution containing 50 Loomis units fibrinolysin and 50,000 units desoxyribonuclease applied topically, for periods of three hours 3 times daily, for seven days. Considerable improvement in fibrinopurulent base of stump.

REFERENCES: (1) Coon, W. W.; Wolfman, E. F., Jr.; Foote, J. A., & Hodgson, P. E.: Am. J. Surg. **98**:4, 1959. *(2) Friedman, E. L.; Little, W. A., & Sachtleben, M. R.:* Am. J. Obst. & Gynec. **79**:174, 1960. *(3) Margulis, R. R., & Brush, B. E.:* Arch. Surg. **65**:511, 1952. *(4) Personal Communications to the Department of Clinical Investigation, Parke, Davis & Company, 1959.*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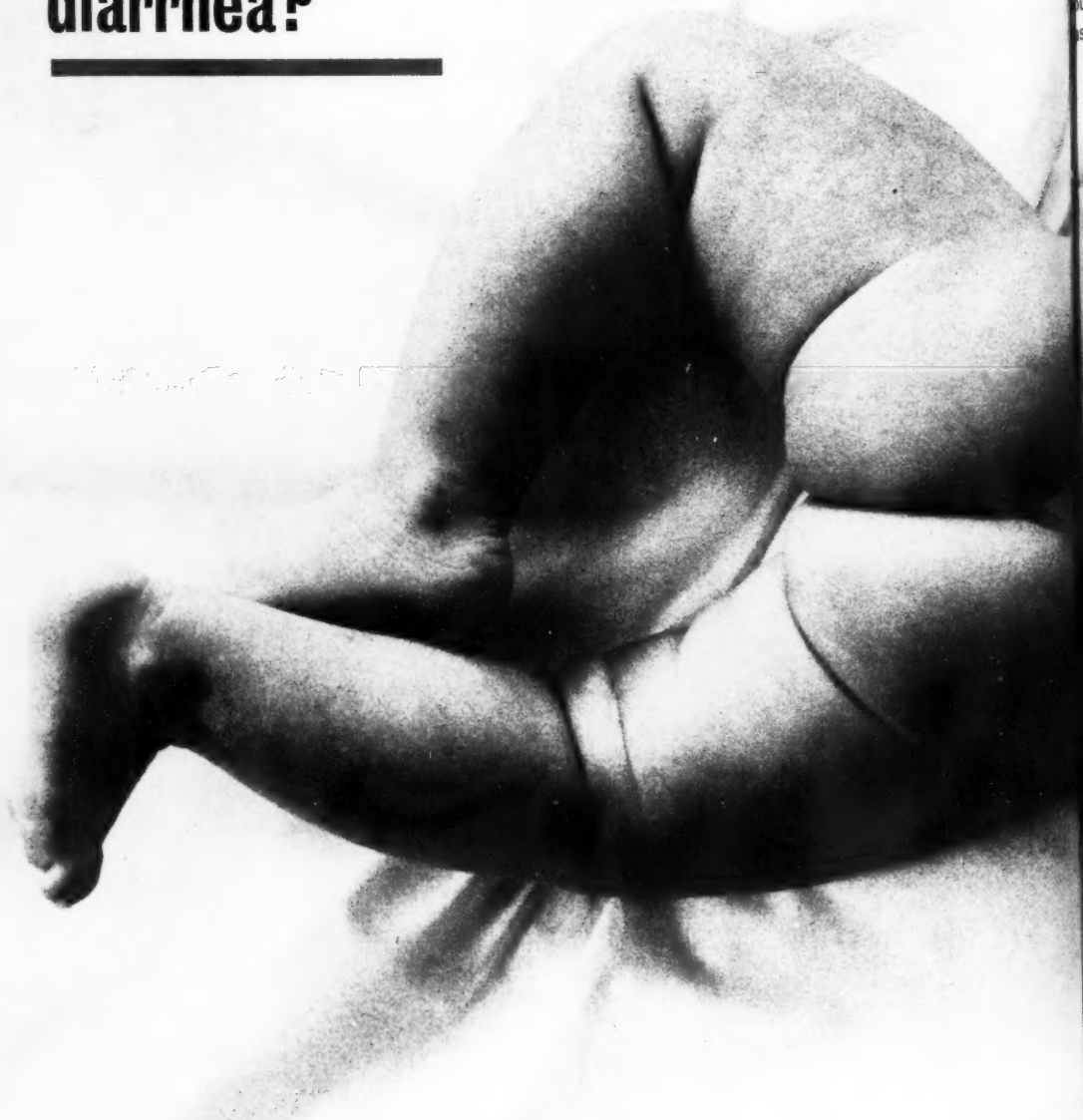
are opiates now outmoded in pediatric diarrhea?



References: 1. Hock, C. W.: M. Times **88**:320, 1960. 2. McHardy, G.; Browne, D.; McHardy, R.; Bodet, C., and Ward, S.: J. Gastroenterol. **24**:601, 1955. 3. Robin, B. A.: Maryland State M.J., in press. 4. Farchione, L. A.: Arch. Pediat., Jan. 19

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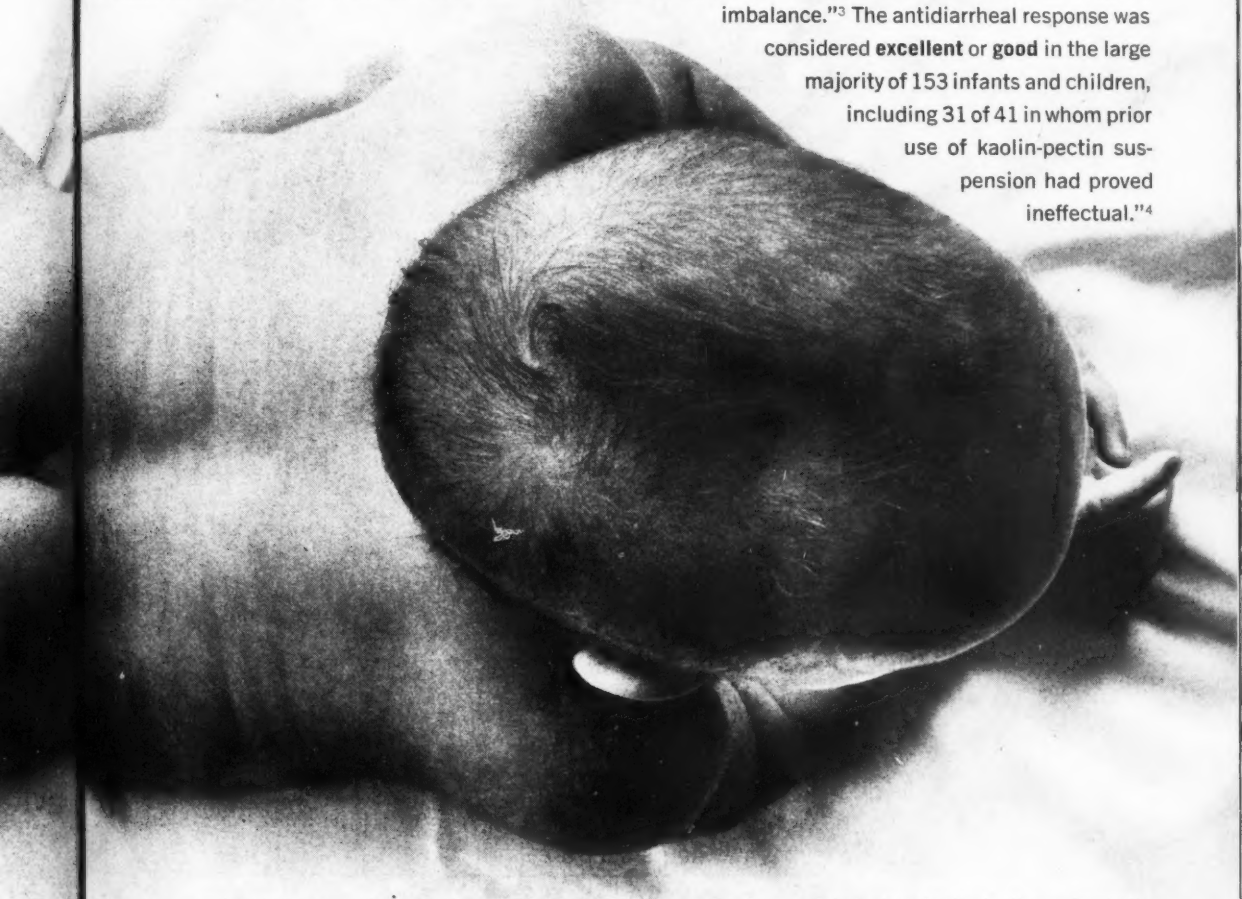

without the undesirable properties of opiates. ENTOQUEL is completely unrelated chemically to the opium alkaloids—it has no addictive or central depressant properties and does not produce undesirable atropine-like effects when administered in the usual therapeutic dosages.[2] In 153 patients, a mild flushing of the skin was the only side effect noted. This occurred in 4% of the total cases and could be eliminated by decreasing dosage.[4]

And when the diarrhea is bacterial in origin

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Smooth, balanced action lifts depression as it calms anxiety...rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.*

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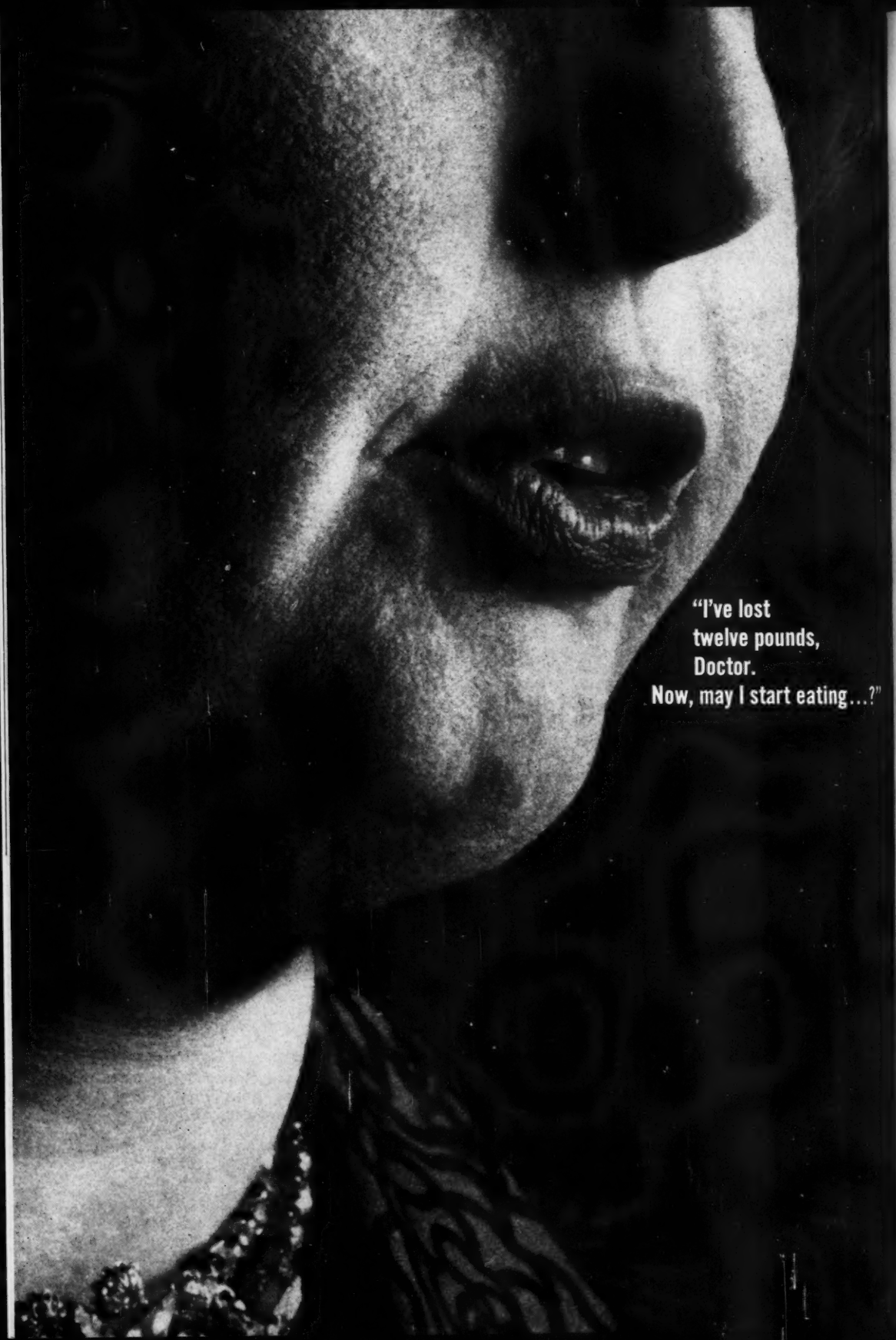
"I've lost
twelve pounds,
Doctor.
Now, may I start eating...?"

"crash diets" do not solve the basic patient problem: habitual overeating

In the treatment of chronic obesity, "fad diets" are not the answer. Your patients may suffer adverse somatic as well as psychic effects from alternating weight loss and gain.
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For demonstrably greater relief in asthma[1]

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CLEARS the bronchial tree of thick mucus and DILATES the bronchioles

Bronkotabs is more effective because it is more comprehensive in treatment. First, Bronkotabs dilates bronchioles, combats local edema and provides mild sedation.

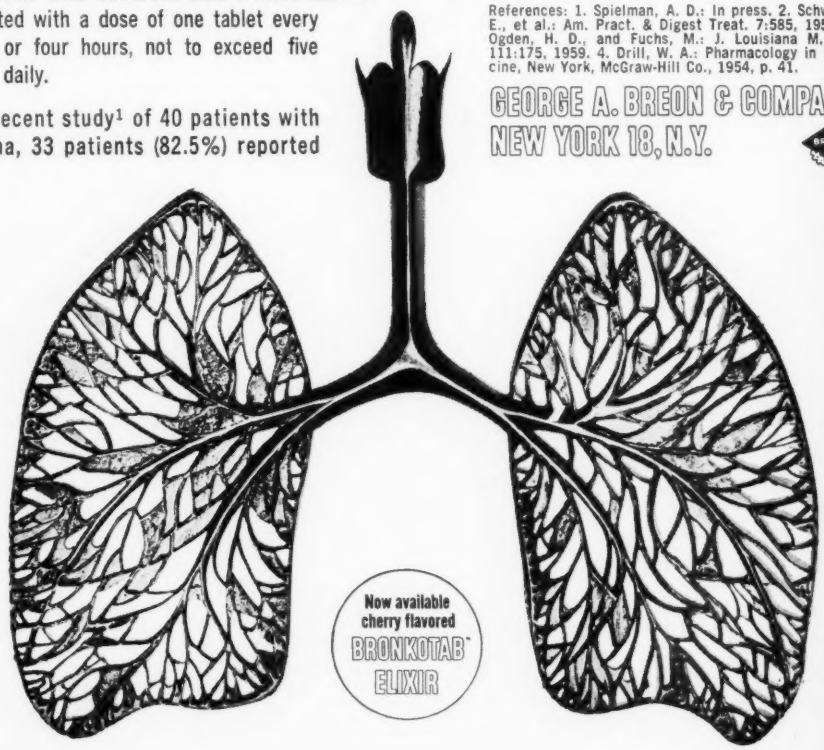
In addition, Bronkotabs decongests, using a most effective expectorant (glyceryl guaiacolate)[2] to liquefy and help expel the thick, tenacious mucus which is the cause of much of the respiratory distress in chronic asthma.[3] Since asthma is a chronic allergic disease of the bronchial tree,[3] Bronkotabs also supplies a highly efficient antihistamine (thenyldiamine) for prophylactic maintenance.[4] Marked and consistent relief of symptoms with minimum side effects can be expected with a dose of one tablet every three or four hours, not to exceed five times daily.

In a recent study[1] of 40 patients with asthma, 33 patients (82.5%) reported Bronkotabs brought fair to good relief from asthmatic symptoms. Asthma relief was expressed by ease of expectoration of secretions, reduction of bronchospasm, and increased vital capacity. "The combination of drugs used in . . . [BRONKOTABS] . . . gave greater relief in these patients than the conventionally used tablet [ephedrine, theophylline, phenobarbital] . . ."

BRONKOTABS DOES MORE FOR THE ASTHMATIC BECAUSE IT IS MORE COMPREHENSIVE IN ACTION. Each tablet contains: Theophylline 100 mg.; Ephedrine Sulfate 24 mg.; Phenobarbital 8 mg.; Thenyldiamine HCl 10 mg. and Glyceryl Guaiacolate 100 mg.
Supplied: bottles of 100 white scored tablets.

References: 1. Spielman, A. D.: In press. 2. Schwartz, E., et al.: Am. Pract. & Digest Treat. 7:585, 1956. 3. Ogden, H. D., and Fuchs, M.: J. Louisiana M. Soc. 111:175, 1959. 4. Drill, W. A.: Pharmacology in Medicine, New York, McGraw-Hill Co., 1954, p. 41.

GEORGE A. BREON & COMPANY
NEW YORK 18, N.Y.



the new high-potency multivitamin from Robins

Adabee: simple as A,B,C,D!

Use simple, sound Adabee to build with. Use it to block anticipated deficiencies before they occur — as in surgery, or to reconstruct depletions brought on by physiologic stress. For Adabee contains only foursquare portions of the basic A, B, C, and D groupings; those most commonly prescribed.[1] And in Adabee, they are present in a combination and amounts that provide efficient, sustained, dietary support too. No extra ingredients, no B_{12}, or folic acid.[2,3] Adabee is easy to remember, simple to prescribe, and kind to your patient's purse. Each yellow, capsule-shaped tablet contains: Vitamin A, 25,000 USP units; Vitamin D, 1,000 USP units; Thiamine mononitrate (B_1), 15 mg.; Riboflavin (B_2), 10 mg.; Pyridoxine HCl (B_6), 5 mg.; Nicotinamide, 50 mg.; Calcium pantothenate, 10 mg.; and Ascorbic acid, 250 mg. Or if you prefer, there's Adabee®-M with eight minerals added.

references: 1. J.A.M.A., 169:41, 1959. 2. J.A.M.A., 173:240, 1960. 3. Federal Register, 25:136, July 14, 1960, p. 6633. 4. Frohlich, E. D., New Eng. J.M., 259:1221, 1958.

PHARMACEUTICALS 1878 RESEARCH

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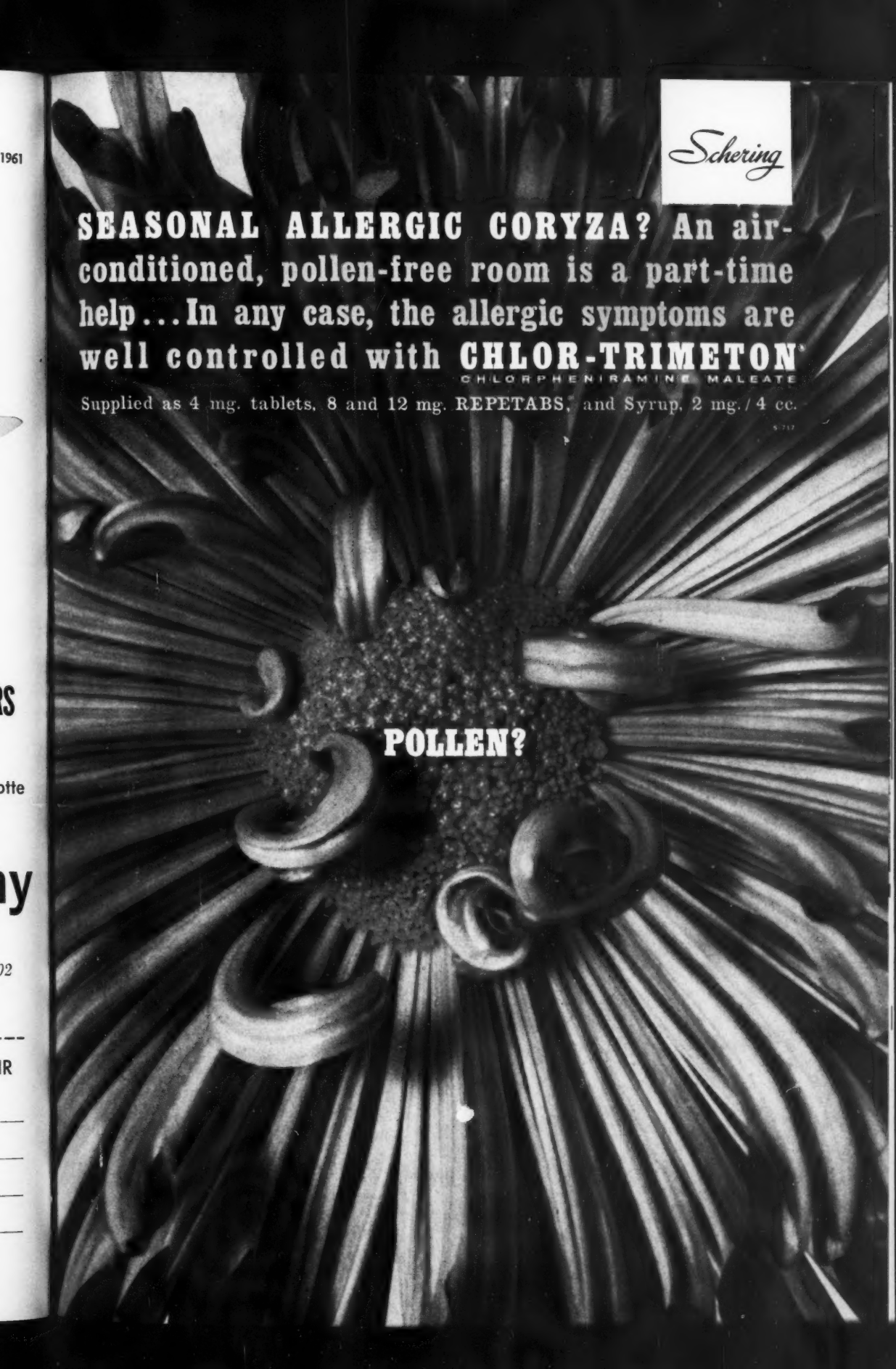
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SEASONAL ALLERGIC CORYZA? An air-conditioned, pollen-free room is a part-time help... In any case, the allergic symptoms are well controlled with CHLOR-TRIMETON®
CHLORPHENIRAMINE MALEATE
Supplied as 4 mg. tablets, 8 and 12 mg. REPETABS,® and Syrup, 2 mg./4 cc.
S-717
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Bed of Digitalis purpurea
with Campanula (Canterbury Bells) in foreground

Not far from here are manufactured
from the powdered leaf
Pil. Digitalis (Davies, Rose)
0.1 Gram (1½ grains) or 1 U.S.P. Digitalis Unit.
They are physiologically standardized,
with an expiration date on each package.
Being Digitalis in its completeness,
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entire therapeutic value of the drug.
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D-37

Percodan tablets effectively relieve pain through a range of

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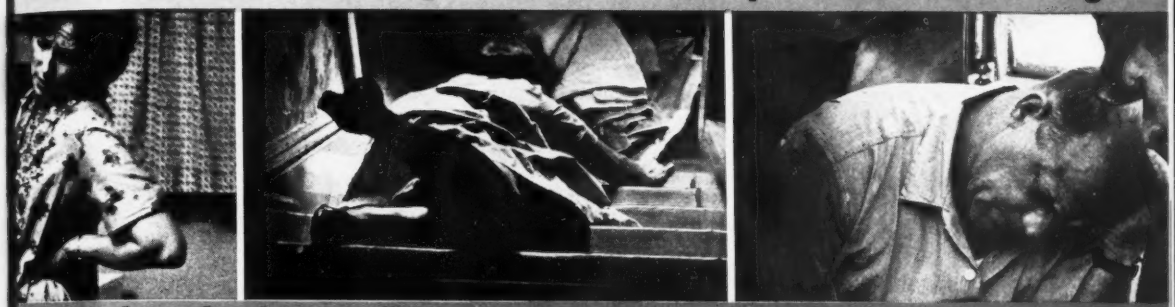


through major traumatic areas into further regions of severe pain

Percodan®

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

TABLETS

for pain

prompt **relief**
profound **relief**
prolonged **relief**

ACTS FASTER—usually within 5-15 minutes. **LASTS LONGER**—usually 6 hours or more. **MORE THOROUGH RELIEF**—permits uninterrupted sleep through the night. **RARELY CONSTIPATES**—excellent for chronic or bedridden patients.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit forming. Federal law permits oral prescription.

Each PERCODAN* Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

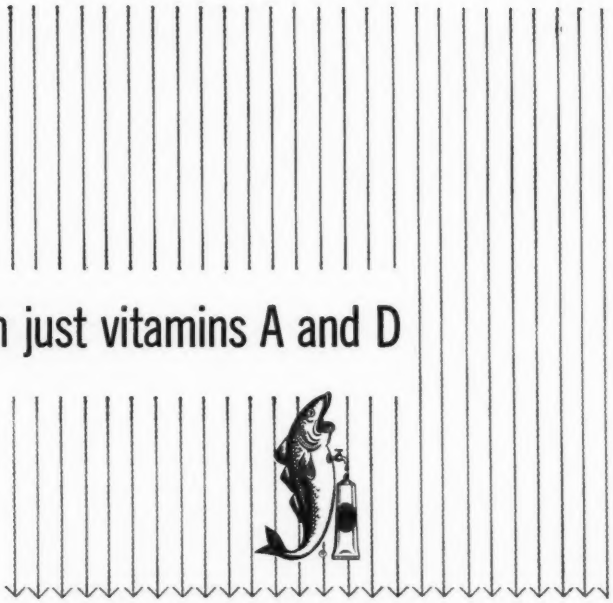
Also available—for greater flexibility in dosage—PERCODAN®-DEMI: The PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

LITERATURE AVAILABLE ON REQUEST

Endo

ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Patent Nos. 2,628,185 and 2,907,768



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also provides
unsaturated fatty acids as well as the vitamins A and D (of high grade Norwegian cod liver oil)—essential to skin health and integrity

and ingredients that are emollient, lubricant, gently astringent, protective, and aid tissue repair (zinc oxide, talcum, petrolatum and lanolin)

in a smooth creamy ointment so processed that one application of Desitin soothes, protects, and promotes healing for hours in . . .

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(decubitus, diabetic, varicose)
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in over six years of clinical use and
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Effective

for relief of anxiety and tension

Outstandingly Safe

1. simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
2. no cumulative effects, thus no need for difficult dosage readjustments
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Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

Also supplied in sustained-release capsules . . .

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Available as Meprospan-400 (blue-topped *sustained-release* capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped *sustained-release* capsules containing 200 mg. meprobamate).

CM-4234

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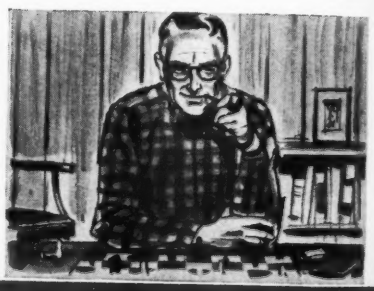
THE HEMATINIC WITH BUILT-IN NUTRITIONAL SUPPORT...



Women of menstrual age, many growing children, blood donors, geriatric patients and convalescents may need a hematinic . . . and all can benefit from Livitamin.

Livitamin offers the ideal formula to restore depleted iron reserves and give nutritional support—an important aspect of iron deficiency.

Iron in Livitamin is well absorbed and stored and well tolerated. B complex and other ingredients provide integrated nutritional support.

And Livitamin is a boon for your taste-fussy patients who *should* but *will not* take a hematinic.

LIVITAMIN®

. . . the hematinic with built-in nutritional support

FORMULA: Each fluidounce contains:

Iron peptonized (equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble, N.F.	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Cobalamin	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

SUPPLIED: Liquid or capsule; also available as capsules, LIVITAMIN with Intrinsic Factor.

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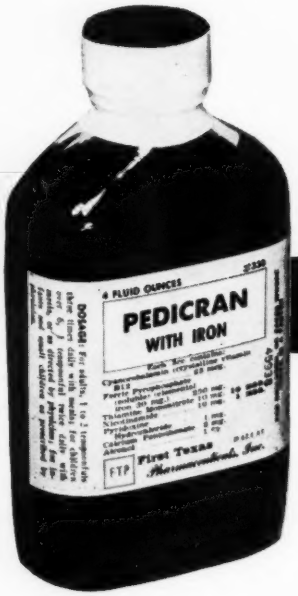
FOR THEIR *Well* BEING



PEDICRAN
with IRON

LIQUID

HEMATOPOIETIC for Hypochromic and Macrocytic Anemias

PEDICRAN WITH IRON provides the hematopoietic effect of vitamin B 12, nutritionally available iron, and vitamin B-complex components to improve appetite, growth and general nutrition, when impaired by vitamin deficiency.

Recommended dosage for adults is 1 to 2 teaspoonfuls three times daily with meals; for children over six, 1 teaspoonful twice daily with meals or as directed by physicians; for infants and small children as prescribed by physicians.

There are no known contraindications when used as directed.

Supplied in bottles containing four ounces and one pint.

Each teaspoonful of Pedicran with iron (5cc.) contains:

Cyanocobalamin (vitamin B 12) .....25 mcg.
Ferric Pyrophosphate (soluble) .....250 mg.
(elemental iron 30 mg.)
Thiamine Mononitrate ..... 10 mg.
Nicotinamide ..... 10 mg.
Pyridoxine Hydrochloride ..... 1 mg.
Calcium Pantothenate ..... 2 mg.
in a pleasing palatable syrup base.

Pedicran with iron is another established need product

in our 61st year . . .

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symptoms gone... feels like a new woman

basic therapy in vaginitis eliminates symptoms · itching · burning · leukorrhea · malodor · destroys pathogens · Trichomonas vaginalis · Candida (Monilia) albicans · nonspecific organisms...alone or in combination · has these advantages · high rates of clinical and cultural cures · effectiveness even in menstrual blood and vaginal debris · safe and nonirritating to delicate inflamed tissue · esthetically acceptable with no disagreeable staining

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Powder / Suppositories

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What now?

Chymar®, for one thing

THE SUPERIOR SYSTEMIC ANTI-INFLAMMATORY ENZYME

to control inflammation, swelling and pain in ACCIDENTAL TRAUMA and general surgery[1-3]

In a study of 491 cases that included 47 fractures, 45 tonsillectomies, 61 herniotomies and 31 cyst removals, it was concluded that: "chymotrypsin reduces or prevents traumatic and surgical edema and hematoma, accelerates absorption of blood and lymph effusions, reduces pain, promotes wound-healing, and may enhance or augment the action of antibiotics."[1]

1. Cigarroa,. L G.: J. Internat. Coll. Surgeons *34*:442, 1960. 2. Teitel, L. H., *et al.*: Indust. Med. *29*:150, 1960. 3. Billow, B. W., *et al.*: Southwestern Med. *41*:286, 1960.

the systemic route to faster healing at any location

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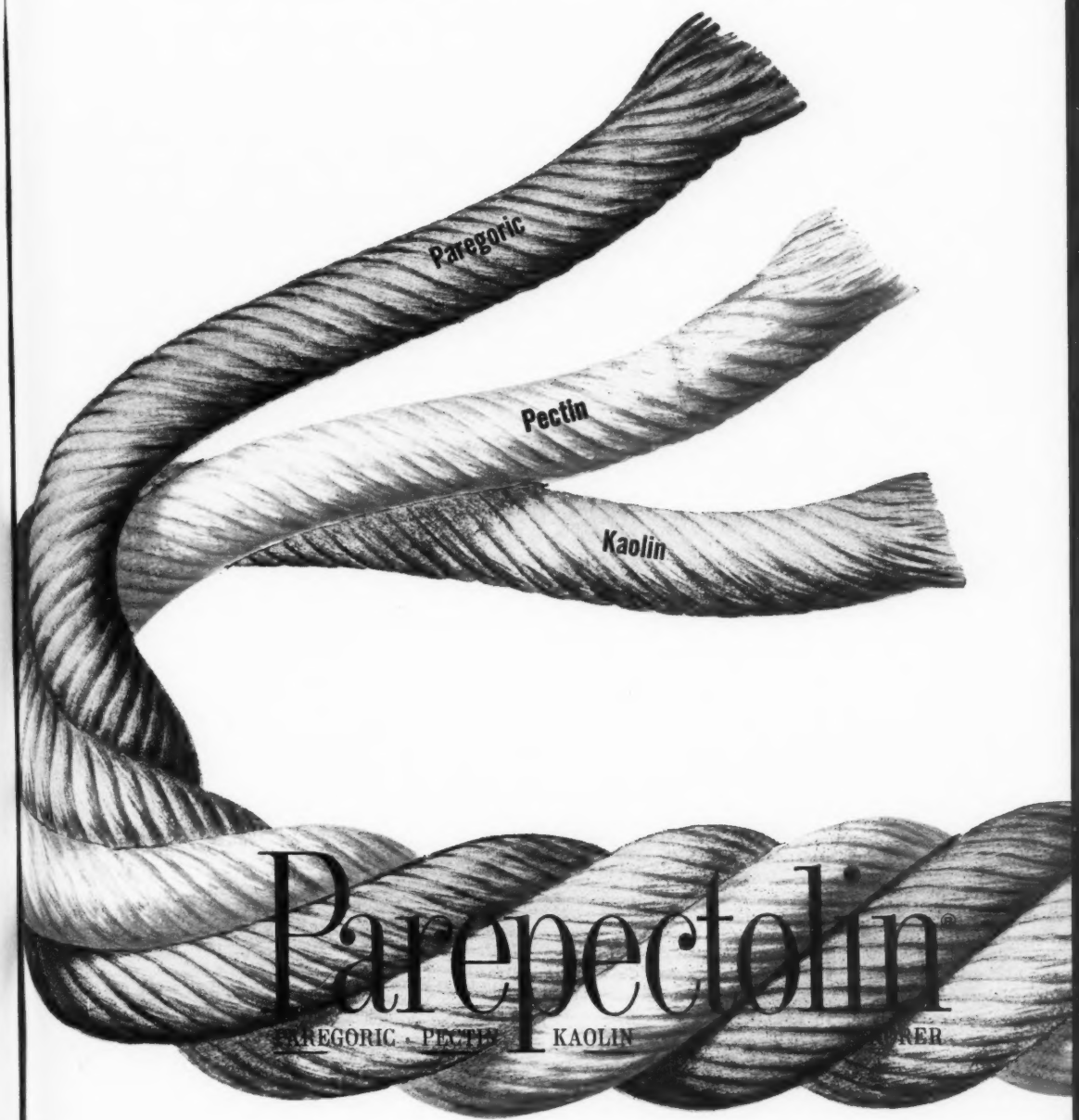
CHYMAR

Chymar Aqueous and Chymar (in oil) contain chymotrypsin, a proteolytic enzyme with systemic anti-inflammatory and antiedematous properties. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac or renal origin; hastens absorption of blood and lymph extravasates; restores local circulation; promotes healing; reduces pain. INDICATIONS: Chymar is indicated in respiratory conditions to liquefy thickened secretions and suppress inflammation of mucosa and bronchiolar tissue; in accidental trauma to speed reduction of hematoma and edema; in inflammatory dermatoses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologic conditions to suppress inflammation and edema and stimulate healing; in surgical procedures to minimize surgical trauma with inflammation and swelling; in genito-urinary disorders to reduce pain and promote faster resolution; in ophthalmic and otorhinolaryngic conditions to lessen hematoma, edema and inflammatory changes; in dental procedures to lessen pain and gum tissue trauma, with inflammation and swelling, in reaction to extractions or surgery. PRECAUTIONS: Chymar and Chymar Aqueous are for intramuscular injection only. Although sensitivity to chymotrypsin is uncommon, allergic or anaphylactic reactions may occur as with any foreign protein. The usual remedial agents should be readily available in case of untoward reaction. Precautions (scratch testing for Chymar, scratch or intradermal testing for Chymar Aqueous) should be exercised in those patients with known or suspected allergies or sensitivities. DOSAGE: 0.5 cc. to 1.0 cc. deep intramuscularly once or twice daily, depending on severity of condition. Decrease frequency as course of condition is altered. In chronic or recurrent conditions, 0.5 cc. to 1.0 cc. once or twice weekly. SUPPLIED: 5 cc. vials, 5000 Armour Units of proteolytic activity per cc.

ONTROL DIARRHEA... the traditional and time-tested triad of effective and safe agents



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olin combines paregoric, pectin, kaolin in *a balanced, stable colloidal suspension,* mooth, creamy consistency and a pleasant, mildly aromatic flavor. Parepectolin atible with antibiotics, and retains its uniform consistency and its good flavor.

Parepectolin; each fluid ounce—Paregoric (equivalent) 1.0 dram, Pectin 2.5 gr., Kaolin (specially purified) 85 gr. Bottles of 4 and 8 fluid ounces.

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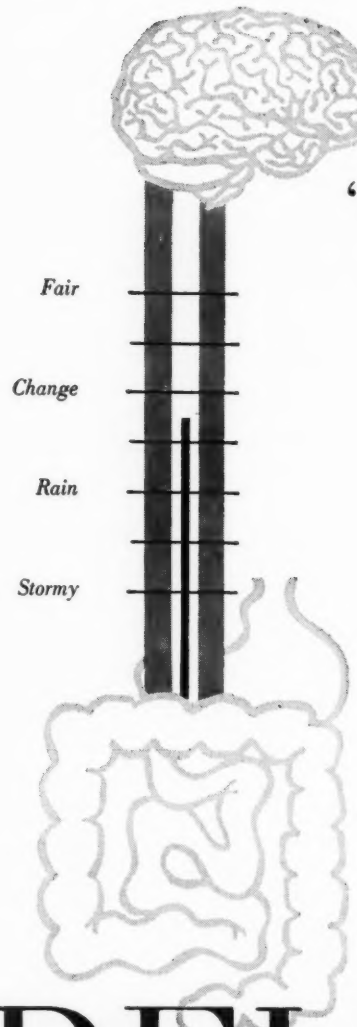

"the G-I tract
is the
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of the mind..."

Belbarb
soothes the agitated mind
and calms the G-I spasm
through the central effect
of phenobarbital and the
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of natural belladonna
alkaloids on the
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20 years of clinical satisfaction

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"be sure to make up more **TRICHOTINE** solution for our examining room."

You can see for yourself the efficient detergent action of Trichotine solution in reducing promptly a cervical plug (using a saturated cotton pledget), or washing away the "cheesy" exudate of monilia.

TRICHOTINE is just as effective for therapeutic irrigation by your patient at home

The same qualities – detergency*, antisepsis, healing – make Trichotine ideal for the treatment of cervico-vaginitis and leukorrheas, alone or in conjunction with other antimicrobials. In the itching, burning, and foul odor of non-specific vaginitis and leukorrhea the action of Trichotine is immediate and gratifying to the patient.

The more you expect of a douche, the more you will use Trichotine in the office and prescribe it for home irrigation, and recommend it as well for postmenstrual and postcoital hygiene.

*SURFACE TENSION: TRICHOTINE 34 DYNES; VINEGAR 60 DYNES; TAP WATER 70 DYNES.

The modern detergent douche

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THE FESLER COMPANY, INC. 375 Fairfield Avenue, Stamford, Conn.

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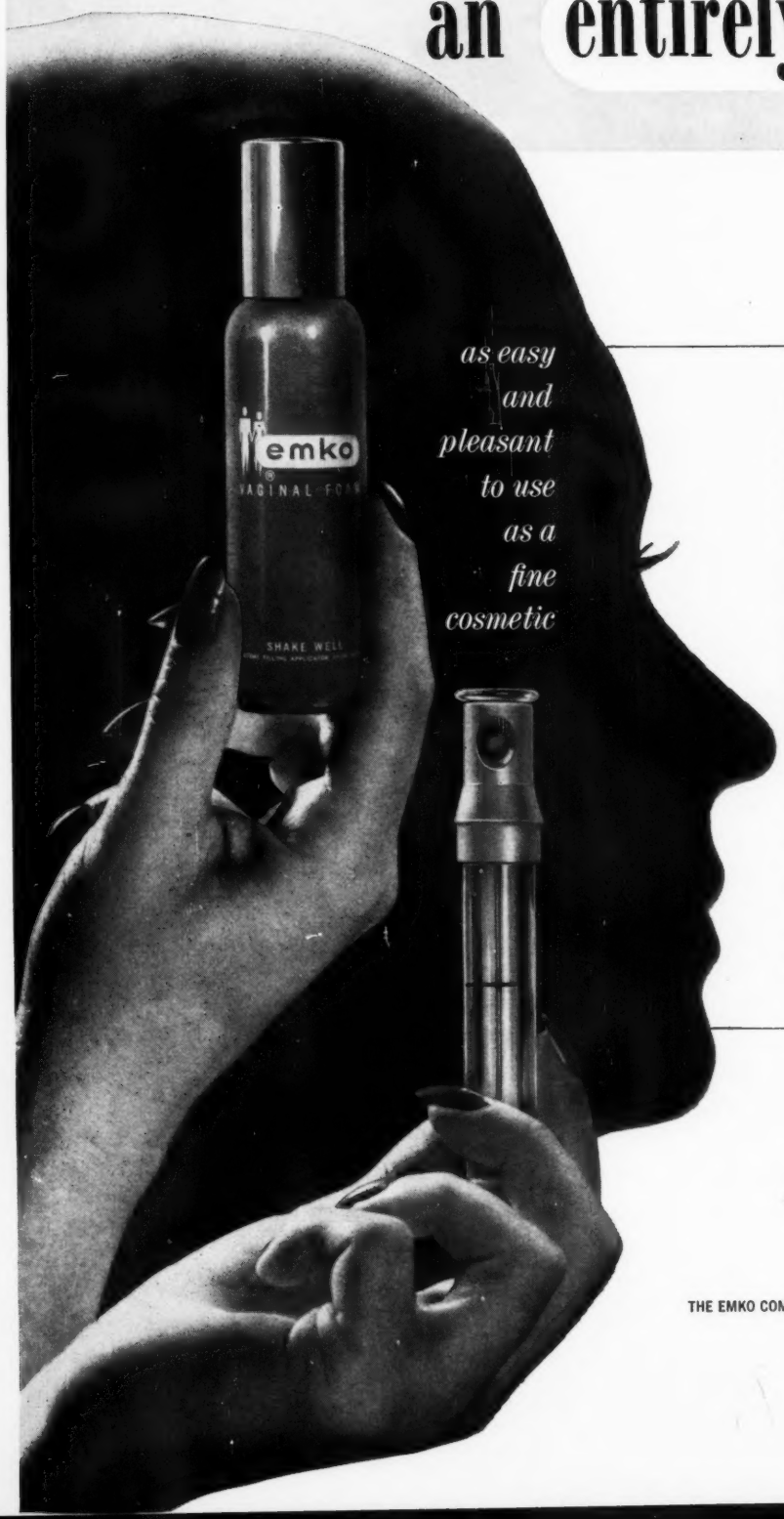

as easy and pleasant to use as a fine cosmetic

EMKO BACKGROUND

Joseph Sunnen, an inventor and industrialist widely known for his philanthropic work, became concerned about the serious economic problems caused by the high birth rate in Puerto Rico. There was an obvious need in that country for a contraceptive more acceptable to the people than the standard creams and jellies.

He suggested combining a proven spermicidal agent with an aerosol foam as a basic carrier. The resulting product, Emko Vaginal Foam, proved simple to use, free of greasiness, and economical.

For the past three years, Emko has been made available in Puerto Rico through the Family Planning Association and the Government Department of Health. Approximately 35,000 families are now using it.

The success of Emko Vaginal Foam in Puerto Rico, and the support it has received from the many people who have visited there, led to the decision to make Emko available to doctors and their patients in the United States.

NOW YOU CAN
PUT YOUR PATIENT'S MIND
AT EASE... WITH EMKO

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pproach to birth control

emko®
VAGINAL FOAM*

using principles never before applied to contraceptives

• THE FIRST AEROSOL FOAM!

The volume of the material is expanded ten times to create A BLOCK OF FOAM.

• THIS BLOCK SEALS THE CERVICAL OS.

Only a FOAM can successfully serve this diaphragm-like function . . . without interfering with normal intercourse or reducing sensory contact.

• A HIGHLY EFFECTIVE PROVEN SPERMICIDE

EMKO Vaginal Foam contains the widely used and thoroughly proven spermicide Nonyl phenoxy polyoxyethylene enthanol 8.0% and Benzethonium Chloride 0.2%.

The total surface area of each bubble of foam contains this highly effective spermicidal combination. As the sperm attempts to penetrate the block of foam, its zig-zag course exposes it constantly to this very large contact area created by the bubbles.

Thus, Emko Vaginal Foam assures maximum spermicidal exposure . . . with a minimum weight of material.

• No douching . . . it vanishes after use **• Absolutely no greasiness or "after-mess"**

• No diaphragm . . . the foam does the blocking **• No irritation for husband or wife**

MARGARET SANGER RESEARCH BUREAU/**INTERIM REPORT**

In the Contraception Service of the Margaret Sanger Research Bureau, through October 31, 1960, Emko had been used from one to 22 months by 362 patients, with a total of 12 unplanned pregnancies. Seven of the pregnant patients admitted irregularity in the use of Emko.

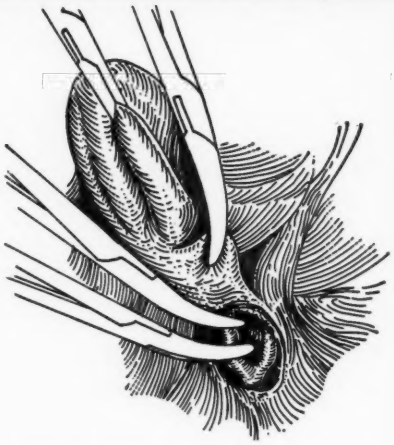
Two planned pregnancies had also occurred after stopping the use of Emko.

A. J. SOBRERO, M.D. *Research Director*

*PAT. NO. 2,943,979, OTHER PATS. PEND.

AN AMES CLINIQUICK®

CLINICAL BRIEFS FOR MODERN PRACTICE



HOW MAY A PATIENT BE REASSURED THAT REMOVAL OF HIS GALLBLADDER WILL NOT SERIOUSLY IMPAIR HIS DIGESTIVE ABILITY?

He may be told that, among animals of similar dietary habits and digestive processes, some have a gallbladder and some do not. Among the herbivores, the cow and sheep have one, the deer and horse do not; among the omnivores, the mouse has one but the rat does not.

Source: Farris, J. M., and Smith, G. K.: M. Clin. North America *43*:1133 (July) 1959.

when the patient needs increased bile flow...

DECHOLIN®

(dehydrocholic acid, AMES)

"Constant loss of bile [from relaxation of sphincter of Oddi following cholecystectomy] reduces the amounts available for lipid absorption after meals, with resulting clinical symptoms apparently relieved by bile acid administration." *Source:* Popper, H., and Schaffner, F.: Liver: Structure and Function, New York, McGraw-Hill 1957, p. 309.

Available: DECHOLIN Tablets (dehydrocholic acid, AMES) 3¾ gr. (250 mg.). Bottles of 100, 500, and 1,000.

and for hydrocholeresis plus *spasmolysis*...

DECHOLIN® WITH BELLADONNA

(dehydrocholic acid with belladonna, AMES)

Available: DECHOLIN Belladonna Tablets: DECHOLIN (dehydrocholic acid, AMES) 3¾ gr. (250 mg.) and extract of belladonna ⅙ gr. (10 mg.). Bottles of 100 and 500.

AMES COMPANY, INC
Elkhart • Indiana
Toronto • Canada

Vertigo is reversible

Antivert® STOPS VERTIGO

moderate to complete relief of symptoms in 9 out of 10 patients'

Prescribe one ANTIVERT tablet (or 1-2 teaspoonfuls ANTIVERT syrup) 3 times daily, before each meal, for prompt relief of vertigo, Meniere's syndrome and allied disorders. Side effects are short-lived, usually only harmless flushing and tingling associated with vasodilation. ANTIVERT is contraindicated in severe hypotension and hemorrhage.

Supplied: Small blue-and-white scored tablets (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.) in bottles of 100. Syrup in pint bottles. Prescription only. Bibliography available on request.

And for your aging patients—
NEOBON® Capsules: five-factor geriatric supplement.

Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

ROERIG

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

now available:

Antivert syrup

Each teaspoonful (5 cc.) contains 6.25 mg. meclizine HCl and 25 mg. nicotinic acid.

uterine relaxation with no side effects

Lutrexin®

TABLETS

(H.W. & D. brand of lututrin)

IN PREMATURE LABOR THREATENED AND HABITUAL ABORTION AND DYSMENORRHEA

LUTREXIN is the protein-like, water soluble, non-steroid uterine relaxing hormone, which decreases uterine contractions within 30 minutes following oral administration.

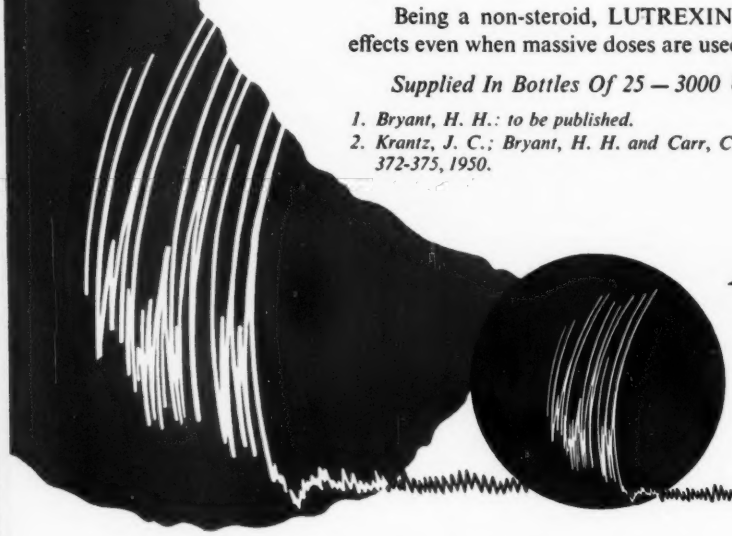
LUTREXIN has been used successfully for the past eight years in thousands of cases of dysmenorrhea, premature labor and threatened and habitual abortion.

Recent animal and laboratory experiments by Bryant[1] demonstrate the almost complete blocking by LUTREXIN of the contracting action of Pitressin and oxytocin on uterine muscle. This complements the bio-assay technique of Krantz, Bryant and Carr[2], which demonstrates how LUTREXIN completely relaxes uterine contractions.

Being a non-steroid, LUTREXIN causes no untoward by-effects even when massive doses are used.

Supplied In Bottles Of 25 — 3000 Unit Tablets

1. Bryant, H. H.: to be published.
2. Krantz, J. C.; Bryant, H. H. and Carr, C. J.; Surg., Gyn. & Obst., 90: 372-375, 1950.



in vivo measurement of LUTREXIN on contracting uterine muscle

HYNSON, WESTCOTT & DUNNING, INC. H&WD **BALTIMORE 1, MARYLAND**

Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

April 1961

Angiography by Brachiovertebral and Temporal Arterial Catheter*

JOSE L. GARCIA OLLER, M.D., N. NELSON, M.D., P. ESPENAN, M.D., W. FERNANDEZ, M.D., C. MATHIRNE, M.D., and W. HAYDEL, M.D.,† *New Orleans, La.*

By direct arterial catheterization, angiography of cerebral vascular supply is successful. The authors summarize their results with this technic.

COUNTER-CURRENT BRACHIAL INJECTION by cannula was first reported by Castellanos and Pereiras[1] in 1939. Gould, Peyton and French[2] recommended this technic in 1955 for vertebral artery angiography in children, and Collins, Slade and Lockhart[3] adapted it to adults. Since 1959 we have been using a simplified technic of brachial arterial catheterization. Kuhn[4] uses a cannula. Porstmann[5] reports a percutaneous brachial arterial catheterization for aortography.

Catheter angiography of the temporal artery was developed by Weiner, Azzato and Mendelsohn[6] in 1958.

Certain recent developments suggest a reevaluation of current percutaneous technics:

1. Increased indications for vertebral angiography:
   a. Negative carotid angiograms in subarachnoid hemorrhage.
   b. Early total angiography in vascular problems.
   c. Occipital and occipitotemporal lesions.
   d. Lesions of the posterior fossa.
2. Need for studies of extracranial as well as intracranial blood vessels in occlusive disease.
3. Angiography after head injuries in children and in critically ill patients.

Catheter angiography of the temporal artery promises freedom in positioning and avoids direct injury to the vessel. Brachial angiography offers routine studies of the vertebral circulation with freedom from spasm and direct injury, plus visualization of the carotid artery. We also utilize a combination of procedures to the right brachial and to the left temporal arteries in one session, which produces an excellent one-stage total cerebral angiogram.

Technic. Brachial arteriotomy is performed, and a No. 15 to No. 18 polyethylene catheter is introduced proximally 7 to 12 inches. Fluoroscopic control is not required. After angiography the arteriotomy is closed with 5-0 silk. No vascular complications have occurred in this series, although the radial pulse is diminished for several days. Twenty milliliters of dye is used per injection, diatrizoate sodium, 50 per cent.*

Catheterization of the temporal artery is performed as described by Weiner and associates though we prefer a distance of intubation of 7 to 10 cm.

Material

Eighty-one catheter angiograms were performed:

Temporal	46
Brachial	35
Brachiotemporal	8

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*Hypaque, manufactured by Winthrop Laboratories, New York, N. Y.

The diagnosis in 61 patients:

Brain tumor	15
Subarachnoid hemorrhage	15
Head injury	10
Cerebrovascular accident	8
Epilepsy, focal	6
Other	7

Incidence of Filling. Thirty-four of the 35 brachial angiograms were successful. The vertebral artery was visualized in all. Combined filling of the carotid and vertebral arteries was seen in all but 2 of the brachial angiograms (Fig. 1).

Forty-two of the 46 temporal angiograms were successful. The 8 brachiotemporal angiograms yielded excellent total angiograms.

Subarachnoid hemorrhage. Fifteen patients with subarachnoid hemorrhage were investigated with 12 temporal and 11 brachial angiograms. The findings were:

Aneurysm, arterial	4
Aneurysm, arteriovenous malformation	3
Intracerebral clot	1
Arterial spasm	1
Vertebral thrombosis	1
No surgical lesion	5

In the arterial aneurysms total angiography was used to rule out multiple aneurysms. Spasm of the basilar artery was impressive in 2 cases, and may explain the presence of palpebral ptosis with ipsilateral pyramidal paresis in the absence of aneurysm. Vertebral and carotid thromboses associated with aneurysm were disclosed (Fig. 2, A and B). Among the arteriovenous malformations, 2 had a significant supply from the basilar artery branches (Fig. 2, C and D).

FIG. 1

Normal right brachial angiogram. Basilar and carotid systems visualized.

FIG. 2, A

Vascular diseases. Occlusion of right vertebral artery distal to posterior inferior branch of the cerebellar artery. Patient with subarachnoid hemorrhage.

Only one temporary aggravation of aphasia occurred, but no other complications or mortality were encountered.

Tumors. Seven temporal and 12 brachial angiograms were performed in 15 patients with tumor as follows:

Meningioma	parasagittal	-1
	temporal	-1
Glioblastoma		-4
Oligodendroglioma		
	lateral and third ventricle	1
	bifrontal	1
Astrocytoma, parietal		1
Medulloblastoma		1
Acoustic		1
Metastatic—cerebellum, skull		2
Unverified		2

Diagnosis of a space occupying lesion was possible in all cases. Circulation in the tumor was clear in the meningiomas (Fig. 3, A), glioblastomas and the oligodendrogliomas. Tumors of the posterior fossa showed marked anterior compression or lateral deformation of the basilar artery.

Lesions of the occipital lobe, midline, and of the posterior fossa tend to be missed by carotid angiograms, but are well delineated by the brachial angiogram because: (1) postcerebral arteries branch from the basilar; (2) basilar an-

FIG. 2, B

Occlusion of left internal cartoid artery in the neck. Patient with carotid cavernous fistula "spontaneously" cured by carotid thrombosis.

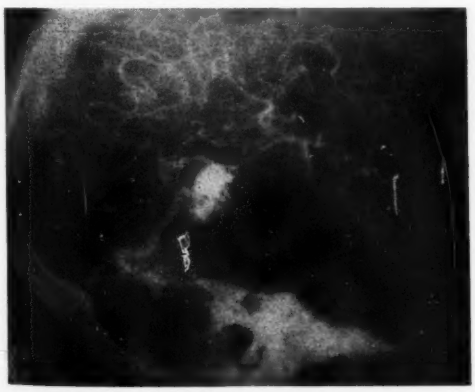
terior and lateral shifts are disclosed; (3) downward basilar compression may indicate tumor of the third ventricle or a temporal pressure cone; (4) the posterior inferior cerebellar artery may show tonsillar hernia; (5) visualization of the posterior choroidal artery may supply intraventricular tumors; and (6) clear venograms of the occipital area and of the vein of Galen and its tributaries are obtained which include the corpus c allo sum circulation.

In 5 of these 15 tumors, visualization of the vertebrobasilar system gave information of tumor which could not have been secured through carotid angiograms.

Angiography in Children. Twelve patients under age 16 had 11 temporal and 3 brachial angiograms, with these findings:

Brain tumor	2

FIG. 2, C



Arteriovenous malformation with intracerebral hematoma. Temporal angiogram.

FIG. 2, D

Arteriovenous malformation. Drainage to the vein of Galen. Absence of branches of carotid and basilar systems to the brain substance.

Acute head injury	2
Subarachnoid hemorrhage	2
Epilepsy, focal	5
Encephalopathy	1

Temporal angiography was performed with ease in these patients. Excellent angiograms by the temporal and brachial routes were obtained in all patients, but in one case only vertebral filling was obtained. An unnecessarily small catheter was used, No. 22.

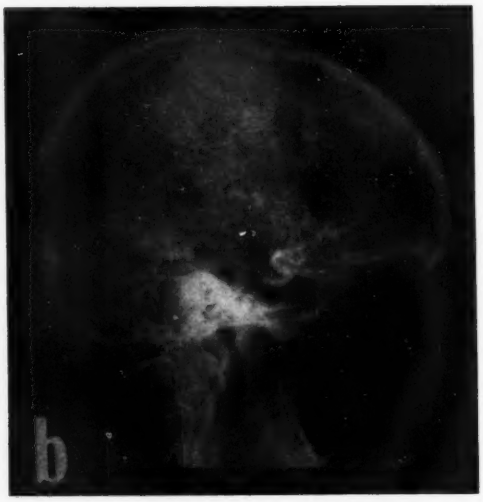
One death occurred in a child *in extremis* having a glioblastoma multiforme. The patient's condition had not improved by ventricular puncture, and ventriculogram was unsuccessful. Angiography was then attempted but could not be completed.

One patient, age 3 years, needed a tracheotomy because of laryngeal edema after the endotracheal anesthetic. The patient recovered, and the tracheotomy tube was removed in one week.

Head Injury. Ten patients having head injury were studied with 12 temporal and 2 brachial angiograms.

Two subdural hematomas were visualized, and one temporal contusion, followed by successful surgical cure. One of the patients having a hematoma showed only bradycardia and headache 3 days after the injury when the angiogram was performed (Fig. 3, B). The patient with contusion showed no localizing neurologic signs, and no clinical indication for operation. He had decerebrate rigidity and hyperthermia of one week's duration when the angiogram was performed.

FIG. 3, A



Meningioma of the convexity. Brachial angiogram.

The opposite situation, where clinically an exploration was indicated, occurred in the following 3 cases:

Case 1. Adult, 8 hours after injury, simple linear skull fracture, with stupor, left hemiplegia.

FIG. 3, B

Space-occupying lesions. Subacute subdural hematoma of 3 days. Temporal angiogram.

Case 2. Adult, simple depressed parietal skull fracture, left hemiplegia. Bilateral pneumonitis, alcoholism, first 8 hours of injury.

Case 3. Child age 3, with Jacksonian epilepsy in status, had a linear parietal skull fracture, stupor, first 2 hours after fall.

In these 3 cases, negative temporal angiography led to conservative treatment. All 3 patients recovered.

Nine of the 10 patients having head injuries in this series recovered. Death occurred in a patient comatose from the time of injury. Negative brachial angiogram with bilateral filling was done 4 hours after injury. The patient made a gradual improvement, but on the seventh day hyperthermia developed and death followed swiftly. Autopsy report indicated a left subdural hematoma.

Negative angiograms were obtained in 3 patients in chronic coma 3 weeks to 6 weeks after head injury. Negative trephination eventually was done. These patients recovered, but not completely. In this group, angiography provided essential diagnostic information not available clinically in at least 4 patients.

Critically Ill Patients. Twenty-eight comatose or stuporous patients were studied with 37 angiograms. Of these 15 had tracheotomy at the time angiography was performed. Pneumonitis, status epilepticus, hyperthermia, decerebrate rigidity, alcoholism, associated maxillofacial injury, were among the complicating conditions found in this group. Successful angiograms were obtained in 27 cases.

Eight patients with head injuries showed successful filling in all cases and no complications occurred in this group, as well as no deaths.

Eight patients having subarachnoid hemorrhage were studied with success in all cases. One patient who had bleeding and partial aphasia prior to the angiogram, developed a temporary aggravation of the aphasia. There was no associated mortality.

Four patients with cerebrovascular accidents were successfully studied and no complications or mortality occurred.

The experience in this group of critically ill patients indicates that angiography is safe and accurate in the presence of head injuries and subarachnoid hemorrhage.

Eight patients harboring brain tumor were studied. One patient *in extremis* with glioblastoma did not survive. Two other patients with glioblastoma died 2 days after angiog-

raphy, after continuing in their comatose condition. For brain tumors in coma, the usual dictum of early operation after the diagnostic procedure should be followed.

Conclusions

1. The catheter angiogram of the brachial artery is safe and reliable for routine vertebral angiography.

2. Temporal catheter angiography is safe and reliable for carotid angiography. It is an excellent technic for pediatric patients.

3. Combined angiography of right brachial-left temporal arteries provides total cerebral and extracerebral angiography at one operative session.

4. Critically ill patients in the categories of head injury and subarachnoid hemorrhage are accurately and safely studied with catheter angiography.

5. Vertebral angiography *per se* gives essential diagnostic data in one third of the cases of brain tumor studied. Catheter angiography is accurate in the diagnosis of a space-occupying lesion, including all the 15 tumor cases studied.

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Discussion (Abstract)

Dr. William F. Meacham, Nashville, Tenn. Dr. Oller and his associates have documented the usefulness of two methods of angiography that have been described previously. Certainly, the accessibility of the superficial temporal artery and the brachial artery simplifies the task of the neurosurgeon in using counter-current injections to demonstrate the intracranial circulation. The greatest appeal to be assigned this technic lies in the ease with which the intracranial vasculature can be demonstrated with but two injections as opposed to the difficulties some of us are still having in obtaining routinely satisfactory carotid and vertebral arteriograms by the method of multiple separate percutaneous arterial punctures.

I would caution against the routine use of the superficial temporal artery route in the older age groups, since it is very likely that in some the arterial lumen will be obliterated or so narrowed and the vessel so tortuous that canalization is impossible or extremely difficult.

In infants and children the method of retrograde brachial angiography is very useful and certainly constitutes the easiest method of obtaining opacification of the vessels on the right side.

Where there is need to demonstrate the origins of the carotids and the vertebral arteries it is likely that direct injections of the subclavian or retrograde aortography constitute the most efficient means of demonstration.

As a neurosurgeon who was "brought up" on the use of air, I cannot help but remind you that in situations where the intracranial pressure has developed to the point of a delicate balance in the compensating mechanisms, any procedure may be associated with a dramatic, disastrous change for the worse. In such cases, access to the ventricular system is imperative, and if angiography is utilized for localization purposes in such patients, it is wise to have a burr opening already in place or the means to perform it at once, if necessary, to facilitate ventricular puncture.

Dr. Oller's presentation is timely and well indicates the practical values of these technics. I subscribe to the philosophies expressed in his paper.

Treatment of Seborrhea Capitis and Associated Diseases*

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The author believes there is an increase in the incidence of hair loss of the scalp in women especially. A number of causes related to current care of the hair are considered as well as prevention and treatment.

THE RELATIVE INCIDENCE OF SEBORRHEA CAPITIS has shown a marked increase in the male and in the female. The etiologic factors suggested are as follows:

Internal causes:

1. Hormonal imbalance.
2. Impaired metabolism and nutrition.
3. Dietary indiscretion, as excessive carbohydrate, and lipid intake.
4. Increased nervous tension.

External causes:

1. Biochemical changes in the cutaneous scalp tissues.
2. Increased number and activity of the resident bacterial and fungal flora.
3. Localized cutaneous inflammatory reactions following the incautious use of topical medication and cosmetics.

Seborrhea capitis, especially the sicca type, is considered to be an exaggerated physiologic process rather than a pathologic entity. No single pathogenic etiologic agent has been singled out although the *Pityrosporum ovale* and various members of the *Staphylococcus* genus have been variously incriminated. Since there are various etiologic and contributing factors, the most satisfactory approach to this problem has been an attempt to control the entity by treating it locally. An actual cure has not been reported. In the search for a better topical agent, we must bear in mind that this preparation is to be used continuously for long periods. Therefore, cosmetic acceptability and nontoxicity are important considerations. We, therefore, must immediately rule out preparations which stain or discolor the hair and scalp and leave an offensive odor or cause the hair to become unmanageable. Also, the patient's desire for a clean scalp naturally makes him prefer a shampoo type of medication in preference to ointments, salves, oils and liquids. Shampoos possess the desirable action of degreasing the scalp and simultaneously removing loose epidermal scales and debris.

I have proposed the following requirements for an ideal antiseborrheic therapeutic agent.[1,2] It should be nontoxic, reduce oiliness, relieve pruritis, have a mild keratolytic action and possess a wide fungicidal and bactericidal spectrum.

After a careful study of the methods being utilized in the topical treatment of seborrhea capitis, it has been learned that there exist 4 methods of application and utilization of antiseborrheic preparations:[2]

1. *The pre-shampoo application* in which a detergent keratolytic is applied to the scalp and remains *in situ* for 5 to 20 minutes. The preparation is then removed by shampooing with neutral soap or detergent.

2. *The medicated shampoo* may contain active ingredients such as sulfur, salicylic acid, resorcinol, hexachlorophene or bithionol, dispersed in the shampoo. This medicated shampoo is applied and left on the scalp from 5 to 30 minutes. It is then removed by addition of water, producing active lathering of the previously applied shampoo with subsequent removal of the medication.

3. *The antiseptic scalp lotion* may contain antiseptics and stimulants, such as resorcinol monoacetate, chloral hydrate, tincture of capsicum, tincture of cantharides, (Vancide) and (Sarthionate). These scalp lotions may also be used as hair dressings.

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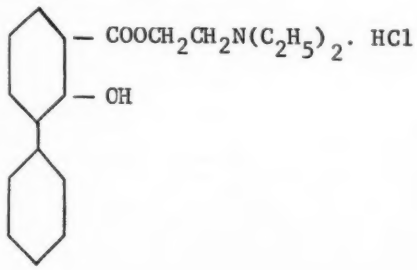
4. *The after-shampoo rinse* is used on the scalp after completion of a shampoo. It is not washed out after the application. The rinse usually contains a quaternary ammonium compound, e.g., benzalkonium chloride.

Recently, during the screening of a new agent for antifungicidal properties, we made the significant observation that biphenamine hydrochloride* effectively controlled seborrhea of the scalp. Inasmuch as the agent was free of sulfur and heavy metals, we decided to investigate it more thoroughly. This report describes the physical and chemical properties and the clinical evaluation of this new drug in the treatment of seborrhea capitis.

Pharmacology

The active ingredient, with the generic name of biphenamine hydrochloride, has the following chemical structure:



It is interesting to note that the structure is similar to salicylic acid which has keratolytic properties, and that it also contains a diethylaminoethanol grouping in the side chain which is generally associated with antihistaminic and antipruritic properties. This compound has profound topical anesthetic action as elicited by application of a 1% aqueous solution applied to the rabbit's cornea and conjunctiva. Effective anesthesia was demonstrated in 30 to 45 minutes. Biphenamine hydrochloride exhibits excellent bacteriostatic and fungicidal activity against a wide range of skin pathogens *in vitro*. Oral toxicity in mice and rats is in the same range as that of acetylsalicylic acid and sodium salicylate. This active ingredient was dispersed in a shampoo base containing triethanolamine lauryl sulfate in an aqueous solution of methocel. The pH hydrogen ion concentration of the shampoo was adjusted to 4.9. This pH was chosen according to the acid-mantle concept of the skin and scalp.

*Alvinine shampoo containing biphenamine hydrochloride 1% was supplied by Dr. William Kremer, Medical Director, Wampole Laboratories, Stamford, Conn.

Clinical Observations

This new shampoo was evaluated in 79 patients who were under treatment for seborrheic disorders of the scalp. Comparative studies of this new medication over an average period of 3 months were conducted with previously used medications. The patient was advised to moisten the scalp, apply one ounce of the biphenamine HCl shampoo to the scalp, leave the solution on the scalp for 10 minutes, then add water to produce a profuse foam, then subsequently remove the foam with the additional application of water. The time interval was usually 10 minutes. Treatments were generally prescribed once a week; however, occasionally for an oily scalp, the patient was advised to shampoo once every 5 days. Subjective relief and objective scalp control were recorded at regular intervals.

Of 79 patients treated, 64 (81.1%) demonstrated the dry or sicca type, 15 (18.9%) the oily type. Falling of the hair and hair loss were additional complaints in 54 (68.3%). Acne vulgaris was present in 15 (18.9%).

Distribution of the seborrheic disorder included the scalp in 79 (100%), brows in 20 (25.3%), the bridge of the nose in 11 (13.9%) and the ears in 2 (2.5%). In 64 (81%) patients, distribution was patchy; in the remainder (15, 19%) it was diffuse. The complaints followed the usual pattern of dandruff: itching in 70 (88.5%), active hair loss in 41 (51.9%) and crusts in 22 (27.8%).

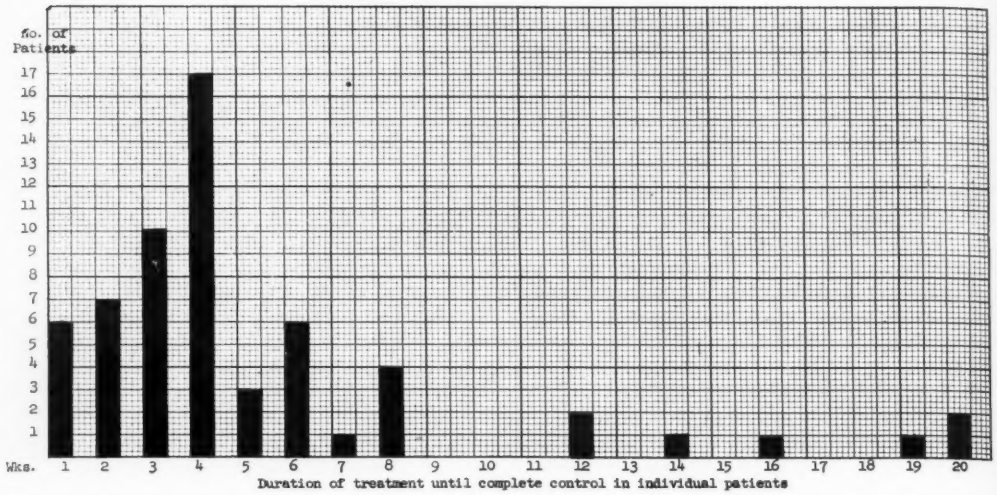
Forty-three males and 36 females were included in this evaluation. The age groups were as follows:

	Males	*Females*
1-10 years	1	0
11-20 "	4	11
21-30 "	22	9
31-40 "	10	6
41 and over	6	10
Total	43	36

Results and Comparison with Previous Therapy

A review of the collected data reveals that there is complete control of seborrhea subjectively and objectively in 61 patients or 77.3%, and partial or satisfactory control in the remaining 18 or 22.5 per cent. In addition, the shampoo possessed cosmetic elegance and was

FIG. 1



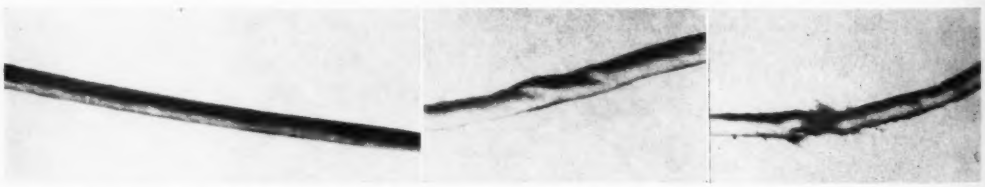
acceptable to the patients. It should be noted that all of the patients had immediate partial relief or improvement, while complete relief and control of the seborrhea capitis was usually obtained within a 4 week period (Fig. 1).

The previous shampoos utilized were selenium sulfide, cadmium sulfide and salicylic resorcin metachlorophene shampoo, and a number of other bland medicated proprietary shampoos. Forty-one of all patients found the previous shampoos unsatisfactory because dandruff was not completely relieved or oiliness of the scalp persisted. Fifteen patients found biphenamine HCl equally as satisfactory as the previously used therapeutic agents. Associated with seborrhea capitis of the scalp, there is occasionally observed folliculitis and falling of the hair. The folliculitis is produced by infection of the pilosebaceous apparatus caused by scratching and rubbing of the scalp. Therapy of the entity usually consists of antiseptic compresses and the use of an antibiotic ointment containing bacitracin, neomycin and polymyxin sulfate. Frequently a corticosteroid, as hydrocortisone, is included with the antibiotics.

The associated hair fall which occurs particularly in the second, third and fourth decade of life may be related to the seborrhea capitis which is prevalent. However, there are conflicting theories as to the direct association of hair fall and seborrhea. In my practice I have observed that frequently the control of the seborrhea capitis may minimize the hair fall in the male.

More recently, the new dermatologic entity of diffuse hair fall in women is being described in the literature. Guy and Edmundson,[3] Sulzberger and associates[4] and Lubowe[2,5] have described the rapidly increasing incidence in the young female of this serious condition. Etiologic factors discussed are: the incautious use of hair cosmetics, permanent waving, hair dyes,

FIG. 2



(A) Normal hair before "permanent and setting"—notice smooth, unbroken line of the hair. (B) Hair set with bobby pins—after shampoo, set and comb-out—shows severe crimping and damage to cortex and medulla. (C) Hair set with bobby pins—after permanent, before comb-out—shows sharp crimping with indentations of cortex (outer layer of the hair) and crushing of the medulla (pulp in center of hair). (Courtesy of Truesdale Laboratories.)

hair tints, hair lacquer, hair curlers and rollers. The latter two mechanical devices injure the cortex and medulla of the hair; the roller particularly produces a traumatic alopecia with possible permanent injury to hair papilla (Figs. 2 and 3).

The use of amphetamines for reducing purposes has also been incriminated. Hormonal studies are being conducted to determine the possibility of endocrinologic dysfunctions. The therapy of this condition has not been established although discontinuance of irritating substances to the scalp is effective in slowing down the excessive hair fall.

Savill[6] has reported the unusual hair fall following the use of hair brushes containing Nylon bristles. Evidently the Nylon bristle has an irregular and sharp end which acts as an irritating mechanical force in tearing out the hair from the hair follicle. Discontinuance of the Nylon brush is followed by subsequent regrowth of hair. However, further studies on a larger number of patients are necessary to properly interpret the effect of Nylon bristles on the hair.

Slepeyan has also reported the thinning of the frontal and parietal area of the scalp by use of the ponytail coiffure. If the ponytail has been used for many years, there may be permanent destruction of the hair follicles with a permanent alopecia. If the use of the ponytail is more recent and is discontinued, the hair follicles become activated again. Teasing of the hair to produce a beehive effect is detrimental to the normal growth of hair. Also, stripping of the hair, which is a removal of one color followed by the introduction of another color or dye during the same processing, can cause a serious effect upon the hair growth. The hair loss is temporary, though continuous processing of the hair in this manner may cause a permanent disturbance in the growth. All of the above factors may be productive in producing the increased incidence of the alopecia which is being observed in the female patient.

FIG. 3

Diffuse hair fall of scalp following several years use of hair rollers and other mechanical devices.

Fortunately, when the etiologic factors which contribute to diffuse hair fall in the female are removed, there is gradual cessation of the alopecia. Rarely does the diffuse hair fall progress to a pattern type of baldness observed in the male.

In laboratory studies conducted in my office on 58 female patients with diffuse hair fall, there were 2 patients who had a blood cholesterol of more than 275 mg. per 100 ml. and one patient had a level 2 mcg. per 100 ml. of protein-bound iodine. This preliminary laboratory study indicates that there is a very minimal degree of alteration in the PBI. and blood cholesterol in the diffuse type of alopecia in women.

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Discussion (Abstract)

Dr. Arthur W. Neilson, St. Louis, Mo. This has been an excellent paper and a beautifully concise discussion of seborrhea capitis and associated diseases, and I would like to congratulate Dr. Lubowe and thank him for coming here and giving it to us. He has been so complete that I doubt that I can add much, but I would like to remark that seborrhea capitis is often seen in patients with no other symptoms of seborrhea, —only the scalp may be involved. The relationship between seborrhea capitis and loss of hair is subject to controversy, and in my reading I have not turned up any real proof that seborrhea influences loss of hair, thought it may be present concomitantly in a majority of scalps. Whereas seborrhea is a disorder of the entire scalp, the loss of hair is usually limited to the characteristic fronto-occipital areas and follows definitely an endocrine hereditary pattern. Seborrhea of the chest

or other hairy areas is not accompanied by loss of hair, nor do we see this typical baldness in women affected with seborrhea. Seborrhea capitis should not be confused with seborrheic dermatitis or seborrheic eczema which is not a disease, but a symptom complex, or a status or habitus influenced by a great many factors. I wish to ask: (1) What do you do in your office when you are confronted by a young woman with diffuse hair fall? (2) Do you feel that hair fall among both males and females is on the increase?

Dr. Lubowe (Closing). There is a marked increase in hair fall and alopecia in women. This feature is discussed more adequately in my book.

Laboratory and physical examinations must be complete. Therapy is prescribed, accordingly, which includes removal of noxious agents (both chemical and mechanical), low carbohydrate-lipid diet, regular shampooing, reduction of tension, use of topical amino acid-estrogen stimulating scalp conditioner, and sustained vitamin-mineral capsule daily.

Fifty-fifth Annual Meeting of Southern Medical Association in Dallas, Texas, November 6-9, 1961

Perforation and Inflammation of Diverticula of the Colon Secondary to Long-Term Adrenocorticosteroid Therapy for Bronchial Asthma and Pulmonary Emphysema*

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The author points to complications in the gastrointestinal tract attendant upon steroid therapy other than the commonly recognized complicating peptic ulceration.

NUMEROUS REPORTS[1-5] have been published dealing with gastrointestinal complications resulting from both the short- and long-term use of the adrenocorticosteroid hormones. It is important that everyone recognize the complications which may occur, and be aware of the dangers involved in their use. We should review the contraindications to use of steroids, particularly those pertaining to the gastrointestinal tract. The great majority of complications reported have dealt primarily with the upper gastrointestinal tract, mainly the formation of peptic ulcers, and perforation and hemorrhage from existing gastrointestinal ulcers.[6] Very little emphasis has been given to the perforation of diverticula following the prolonged use of steroids. In a report on the use of steroid therapy in rheumatic diseases, a description[7] is given of some of the more common complications to the prolonged administration of adrenal cortical steroids.

The masking of infection is not uncommon, perforation of a diverticulum can occur only to be recognized too late to save the life of the patient. In this report I will present 3 instances of ruptured diverticula of the colon and one of severe inflammation with 3 deaths, 2 of which might be directly attributed to the prolonged use of steroids.

*Read before the Section on Allergy, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

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Material

The clinical course of 4 men, varying from 48 to 74 years of age, was followed from October 1957 to April 2, 1960 (Table 1). All had a history of wheezing and shortness of breath for many years. They were all classified as having bronchial asthma and pulmonary emphysema. The patient in Case 1 had been on steroid therapy since April 2, 1951, in Case 2 from March 29, 1958, in Case 3 since May 11, 1954, and in Case 4 since March 17, 1959. None of the patients gave a history of previous gastrointestinal disease, though evidence of a healed duodenal ulcer was found in Case 4 at autopsy. Diverticula were found in all 4 patients, in 3 of whom they were ruptured and in one presented marked inflammation. The patient in Case 4 was found to have an obstructing carcinoma of the transverse colon which was removed. All patients were operated upon and 2 autopsies were performed.

Case Reports

Case 1. A 62 year old man was seen for the first time on April 7, 1959, for wheezing and dyspnea. He had been taking steroids for severe bronchial asthma continuously since April 2, 1951. He had been under the care of allergists in the past and had received hyposensitization therapy with moderate relief. He had been advised to discontinue the steroids because of hypertension.

On physical examination, he was found to have B.P. of 160/100, T. 98.6°F., R. of 24, and P. of 80. The mucous membranes of the nose were pale and swollen with evidence of polypoid change being present. There

TABLE 1

ANALYSIS OF CASES

Case No.	*Age of Patient*	*Length of Time on Steroids*	*Date of Onset of G.I. Symptoms*	*Signs and Symptoms in the G.I. Tract*
1	62	April 2, 1951 (8 yrs., 2 mos.)	July 2, 1959	Abdominal pain, fever, localized tenderness
2	60	March 29, 1958 (2 yrs., 7 mos.)	Feb. 7, 1959	Abdominal pain, distention, localized tenderness
3	48	May 11, 1954 (5 yrs.)	March 25, 1959	Abdominal distention, silent bowel
4	74	April 17, 1959 (1 yr.)	March 21, 1960	Nausea, weakness, anorexia, loss of weight, epigastric pain

was slight wheezing on cough and on deep breathing. The breath sounds were decreased. There was no enlargement of the heart and no murmurs were present.

Allergy skin tests were done and he was found to be sensitive to numerous inhalants, pollens, and foods. Hyposensitization therapy was started on April 16, 1959, with gradual reduction in the dose of the dexamethasone-21-phosphate he had been taking. Each reduction below his maintenance dose would precipitate an acute episode of asthma.

On July 2, 1959, he was admitted to the hospital with pain in the lower abdomen. He had had slight gastrointestinal upsets in the past, but previous roentgenologic studies had revealed no lesions. The condition became progressively worse with pain, nausea, vomiting, and fever. There was some evidence of localized tenderness in the lower abdomen. X-ray films of the abdomen in the recumbent and upright positions demonstrated no free air under the diaphragm. No evidence of intestinal obstruction was visualized. A normal gas pattern in the colon was seen with some air in the stomach. On July 5, at operation a large perforation was found in the sigmoid colon secondary to a ruptured diverticulum. A colostomy was performed and the patient tolerated the procedure quite well. He had been given an increased amount of preoperative steroids which had been continued postoperatively. Following a stormy postoperative course, the patient died on July 17.

Case 2. A 60 year old man was first seen by me on March 28, 1958, in consultation in the hospital, because of marked dyspnea and wheezing. He had become progressively worse in the past 3 years. History revealed a story of hay fever and asthma all his life. Upon physical examination he was found to be markedly dyspneic, cyanotic, and having slight cardiac failure. Treatment for status asthmaticus and heart failure was instituted. Relief was slow until steroids, both intravenous and oral, were used. Intermittent positive pressure breathing was used with mucolytic and bronchodilating drugs. Twelve days after this admission the patient was discharged. He continued a program of hyposensitization, bronchodilators, steroids, and intermittent positive pressure breathing at home, doing quite well.

On Feb. 7, 1959, almost one year after the first admission, he developed generalized pain over the lower abdomen. Because the pain was not severe he continued with symptomatic medication for 9 days, under the care of his family physician. He was seen by us on February 12, and admitted to the hospital with an "acute abdomen." There was pain and tenderness over the entire lower abdomen, slight fever, nausea, and vomiting. The patient had been continued on his steroids. A plain film of the abdomen demonstrated considerable air in the stomach and gas in the ascending transverse, and upper descending colon (Fig. 1). There was a prominent area in the right lower quadrant which was devoid of any gas filled loops of large or small bowel. This was thought to be a periappendiceal abscess or some soft tissue mass. The terminal ileum contained a small amount of gas and had the appearance of a paralytic ileus.

The patient was operated upon on February 13, and a pelvic abscess due to a ruptured diverticulum was found. A right transverse colostomy was performed. A partial small bowel obstruction developed which was relieved later. The patient was continued on steroids. Two months after this admission, the patient returned to have the colostomy closed. Since then and up to the present, he has used routine hyposensitization therapy,

FIG. 1

Flat plate of abdomen showing absence of any gas filled loops of large or small bowel.

bronchodilators, oral dexamethasone, intermittent positive pressure breathing, and is living and well.

Case 3. A 48 year old man was first seen by me April 23, 1958, with severe wheezing and dyspnea. He had been using steroids since May 11, 1954. He complained of pain over the left lower anterior chest, especially on coughing and gave a history of having had asthma since age 4 and had been on symptomatic therapy all his life. The patient was markedly dyspneic on slight exertion and refused hospitalization.

On the physical examination, he was found to have a B.P. of 110/74, T. of 98.6° F., P. of 86, and R. of 40. The mucous membranes of the nose were pale and swollen. There was marked tenderness over the left lower anterior chest, localized in the area of the sixth rib. The heart rate was increased but no murmurs were found. The breath sounds were decreased and wheezing could be heard throughout the lungs. A chest x-ray revealed a fracture of the left sixth rib.

After the acute episode of asthma was controlled by increasing the doses of steroids, allergy skin tests were performed. A program of hyposensitization, use of bronchodilators, and intermittent positive pressure breathing exercises using mucolytic drugs was instituted. He was weaned off the steroids and did very well until May 23, 1958. Because of increasing dyspnea and wheezing he had taken prednisolone, the dosage was increased and he felt better. In spite of the reduction in the maintenance dose he developed considerable pain and discomfort in the epigastric region. On June 6, 1959, because of progressive epigastric discomfort, he was changed from prednisolone to dexamethasone, after x-ray studies of the gastrointestinal tract revealed no evidence of disease.

On March 22, 1960, the patient developed acute lower abdominal pain. He was distended and was unable to move his bowels. Plain film of the abdomen was interpreted as normal. At operation on March 26, and in addition to congenital adhesive band obstructing the intestine, an area of diverticulitis was observed. The patient had received preoperative and postoperative steroids. Following an uneventful convalescence, he was maintained on small doses of triamcinolone for a short period of time and then this was discontinued.

Two months later, on May 22, the patient was admitted to the hospital following an alcoholic overindulgence. He was markedly dyspneic and cyanotic. The heart rate was very rapid and the EKG. showed a superventricular tachycardia. In spite of all efforts of therapy, he died on May 25. Autopsy revealed evidence of chronic bronchial asthma, pulmonary emphysema, hypertrophy of the right ventricle, but no abnormality of the gastrointestinal tract. The adrenal glands showed mild congestion but no atrophy.

Case 4. A 74 year old man was first seen on Oct. 15, 1957, because of continuous wheezing and dyspnea. He had been under the care of an allergist for 20 years. He had received hyposensitization and symptomatic therapy over this period. His general condition had gradually become worse.

In January 1958, he was started on intermittent positive pressure breathing, receiving 3 treatments daily. He got along quite well until April 17, 1959, when he became markedly dyspneic and had severe wheezing. He was admitted to the hospital and steroids were given intravenously along with aminophylline in 5% dextrose solution. He improved rapidly and was discharged 2 weeks later on oral steroid therapy.

The dosage was maintained until March 23, 1960, when he developed nausea and refused to eat. He was hospitalized on March 23, because of loss of weight and slight bleeding from the rectum. Physical examination revealed a white man, sitting up in bed, having difficulty in breathing, and with moderate pallor. P. was 88, R. 30, and B.P. 94/70. The skin was dry and swollen; there was pitting edema of the ankles and the face was swollen. The P-A diameter of the chest was increased, and the x-ray examination revealed emphysema (Fig. 2). Breath sounds were decreased over the entire chest and there was an expiratory wheeze. The abdomen was tender but soft; the liver and spleen were not palpable. Rectal examination presented no masses. A barium enema revealed a mass in the distal one third of the transverse colon strongly suspicious of a malignancy (Fig. 3). There was marked diverticulosis of the sigmoid and lower descending colon.

At operation, on April 1, an obstructing carcinoma about the size of a baseball and one the size of an egg were found. The entire transverse colon was resected and an anastomosis was performed. He had received preoperative and postoperative steroids. The patient improved for about 6 days postoperatively until he again refused fluids and food. His course was one of deterioration and he expired on April 13. At autopsy, a large healed ulcer was found in the duodenum. There was a large leak in the area where the surgical anastomosis had been made. An area of severe diverticulitis with evidence of rupture was found in the

FIG. 2

Marked pulmonary emphysema with flattening of the diaphragm.

FIG. 3

Demonstration of diverticulosis and tumor.

lower descending and sigmoid colon. The adrenal glands showed no evidence of atrophy.

Results

Four cases (Table 2) of diverticulitis associated with ruptured diverticula are reported. All the patients were operated upon and 2 cases came to autopsy. One patient was found to have a healed duodenal ulcer at autopsy and a carcinoma. Each patient developed a complication following operation and 3 died a short time later. One patient is living and well and does not use steroids. He is being maintained on bronchodilator drugs and intermittent positive pressure breathing, using mucolytic agents.

Discussion

Our attention has been frequently called to the hazards and contraindications associated with the use of steroids.[4-8] A recent report showed that triamcinolone therapy did not increase the incidence of peptic ulcerations.[9] However, many unusual gastrointestinal complications have been attributed to the use of adrenal cortical steroid therapy in patients who had no previous gastrointestinal disease.[5] Among these are massive gastrointestinal hemorrhage, perforation of the stomach, perforation of the cecum and colon, and the production of acute duodenal ulcers.

Perforations of the large bowel have been reported in the treatment of cases of ulcerative colitis with steroids. Recently, 4 cases were reported presenting a pathologic picture of ulcerative colitis arising in an area in which diverticulitis had previously existed.[10] These cases raise the possibility that diverticulitis may "trigger" ulcerative colitis and progress to a condition indistinguishable from it. Whether the long-term use of adrenal cortical steroids alters the lesion, in asymptomatic diverticula, is not known. It has been shown experimentally in rabbits and rats that animals treated with cortisone and subjected to asceptic wounds show a marked decrease of actively proliferating fibroblasts as compared with controls.[11,12]

This mechanism which may permit injury of the bowel by the use of steroids is not understood since the bowel is not exposed to gastric secretions. It has been suggested that factors which promote resistance to ulceration in the normal gastrointestinal tract may be suppressed by these hormones.[13]

TABLE 2

RESULTS OF OPERATIONS AND AUTOPSY FINDINGS

Case No.	*Diagnosis*	*Surgical Findings*	*Results*
1	Perforation of a diverticulum of sigmoid colon; pulmonary emphysema	Large perforation of lateral aspect of the sigmoid colon	Patient died, no autopsy
2	Pelvic abscess due to ruptured diverticulitis; pulmonary emphysema	Pelvic abscess due to rupture from diverticulitis	Patient living
3	Diverticulitis with bowel obstruction; pulmonary emphysema	Bowel obstruction due to adhesive band and diverticulitis	Patient died. Autopsy—no adrenal atrophy
4	Diverticulitis, carcinoma of the colon; pulmonary emphysema	Adenocarcinoma of transverse colon, and diverticulitis	Patient died. Autopsy: healed duodenal ulcer; adenocarcinoma of transverse colon; no adrenal atrophy

To those complications of the gastrointestinal tract which have already been reported and due to the long-term use of adrenal cortical steroids, we add perforation and inflammation of the diverticula of the colon.

Summary

Four cases of ruptured diverticula of the colon in persons with bronchial asthma and pulmonary emphysema are presented. Perforation and inflammation of the diverticula are shown to have occurred following the long-term use of steroids. The complications occurred in patients who had had no previous gastrointestinal disease. It is thus seen that care is necessary to observe the lower gastrointestinal tract as well as the upper when using these hormones. It has been well stated that the physician must still estimate whether the anticipated gains in each case exceed the risk of serious, adverse side effects.[14]

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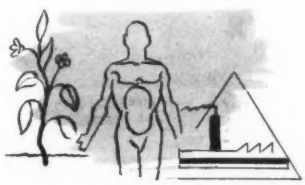
Discussion (Abstract)

Dr. Theodore J. Haywood, Houston, Tex. I would like to congratulate Doctor Fein for his excellent paper, and for bringing to our attention what, I believe, may be a newly recognized, serious complication of long-term corticosteroid therapy. We all know that the presence of gastric or peptic ulcer is one of the major contraindications for corticosteroids, and that rupture of the gastrointestinal tract at the site of ulcerative colitis and regional enteritis has been amply demonstrated. However, Doctor Fein has presented something new, namely, perforation of diverticula of the intestinal tract associated with long-term corticosteroid therapy. The dangers in such a situation are further complicated by the fact that the drug seriously masks the clinical signs and symptoms of peritonitis. Although it is possible that the occurrence of complications in the gastrointestinal tract in Doctor Fein's series of patients receiving corticosteroids is entirely by chance, his paper strongly suggests that the administration of these hormones may be a causative factor. That it is not the only factor is apparent from the large number of patients who receive these agents and who do not experience such complications. Doctor Fein's paper has added evidence to that which we now have available to emphasize exercise of caution in the administration of these agents, and the importance of close supervision of patients receiving them.

Once again, I would like to thank Doctor Fein for such an excellent paper.



Patients with Four or More Cesarean Sections: Second Series*

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The authors have made a second study of multiple cesarean sections and the results of such. The multiple section does not seem to enhance morbidity or mortality.

IN 1955, we reported clinical experience with 130 patients having had four or more cesarean sections.[1] At this time, we present an additional series of 710 patients making a grand total of 840 patients in this category.

As before, this study represents the results of a questionnaire sent to representative hospitals having 25 or more bassinets and distributed evenly geographically over the United States and Canada. Our first report and study was limited to religious hospitals in which sterilization is forbidden insofar as the removal or destruction of normal tissue is concerned, but this present report includes also a small but significant percentage of nonsectarian hospitals.

We owe the original idea prompting this study to Douglass[2] who asked, "What happens to the woman who has had four or more cesarean sections?" He questioned the routine practice of sterilizing a woman who has had two or three sections. In addition, Cosgrove[3] provided another stimulus when he made this provocative statement: "There should be no limit to the number of cesarean sections provided the integrity of the uterus is maintained." We believe our first series justified this contention and now, after further studies comprising this second series, we once again subscribe to his idea.

Tables Showing the Similarity Between the Two Series

Table 1 reveals the obvious similarity of the two series and graphically illustrates that a significant number of women (840) with impaired obstetric capabilities can have families larger than the national average by the utilization of multiple (4 or more) cesarean sections. With the evidence we have accumulated we believe this can be done with safety for all.

TABLE 1

First Series		*Second Series*
130	Cases	710 Cases
464	Previous sections	2,512 Previous sections
44	Vaginal deliveries	190 Vaginal deliveries
638	Babies	3,850 Babies
4.57	Sections/patient	4.56 Sections/patient
5.9	Babies/patient	5.8 Babies/patient

Total

840	Cases
2,976	Previous sections
234	Previous vaginal deliveries
4,488	Total babies born

The failure of the number of previous sections and the number of vaginal deliveries to make the sum of 3,850 babies born in the second series is explained by the fact that the mode of delivery was not reported in some cases of known births.

This striking similarity continues in a comparison of parity incidence (Table 2). Both series show a precipitous drop after the fifth section. Previously we had offered the suggestion that possibly the necessity of delivery by section caused babies to be spaced over a wider span of years. This more recent failure to penetrate higher levels of parity seems to bear out such an idea despite the ever-in-

TABLE 2

		Series 1	*%*	*Series 2*	*%*
4	Sections	84	64.6	458	64.5
5	Sections	30	23.1	165	23.2
6	Sections	9	6.9	53	7.4
7	Sections	5	3.8	27	3.8
8	Sections	0	0.0	5	0.59
9	Sections	1	0.7	2	0.28
10	Sections	1	0.7	0	0.00

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creasing safety and incidence of cesarean section.

Other influential factors might be:—

Fear of rupture
Observation of defective scar
Hysterectomy
Advice of obstetrician
Advancing age
Diminished fecundity
Not enough time elapsing for such multiple sections to be accepted by the physician.

If one accepts the premise that there still exists a certain degree of unfounded or unjustified fear on the part of both the doctor and patient and that clinical judgment of defective scar leaves much to be desired, it is possible that, given time, this suggested wider acceptance of multiple section could increase the average level of parity.

We also believe that only an actual increase in the incidence of the sixth section will disprove the contention that these patients possess a diminished fecundity.

The summation of the grand totals for both series (Table 2, A) with relation to section parity again illustrates the sharp drop in incidence following the fifth section.

The greatest age group difference between the two series (Table 3), is within the group 26 to 30. Pure conjecture might conjure up the thought that this could possibly reflect a trend toward allowing more than three sections and that it would most likely occur at this age level.

Original operative indications (Table 4) seem to have a like similarity with regard to disproportion, an increase with hemorrhage, a decrease with toxemia and an increase with regard to fetal indications. If we consider hemorrhage as largely accidental and recognize the increased trend of section for fetal indications we once again could agree that this is a statistically acceptable series of indications for cesarean section. It does not appear to be feasible to question the collective thinking of so many in this day of adequate preoperative consultation and well-trained operators. But we hasten to bring to mind the statement of Ferguson and Reid[4] that the indication for the first section is the most important single factor in the prevention of rupture of cesarean section scar.

A study of fetal weights (Table 5) indicates the risk of prematurity is greater in patients with multiple cesarean sections but we must also repeat that the risk of rupture, either spontaneous or that caused by uterine distention and/or labor must be weighed against the calculated risk of prematurity. We suggest that this is as it should be and that, in the absence of untoward symptoms referable to the scar, the size of the baby should be the

TABLE 2, A

	Combined Series	
4 Sections	542	64.52%
5 Sections	195	23.21%
6 Sections	62	7.38%
7 Sections	32	3.80%
8 Sections	5	0.59%
9 Sections	3	0.35%
10 Sections	1	0.11%

TABLE 3

Age This Section	*Series 1*	%	*Series 2*	%
Unknown	0	0.0	3	0.42
16-20	0	0.0	2	0.28
21-25	8	6.2	58	8.17
26-30	25	19.2	203	28.67
31-35	48	36.9	247	34.78
36-40	37	28.5	144	20.28
41-45	12	2.3	51	7.1
46 and over	0	0.0	2	0.28

TABLE 4

ORIGINAL OPERATIVE INDICATIONS

	Series 1	*Series 2*	*Total*
C-P disproportion	73	390	463
Hemorrhage	16	112	128
Toxemia	9	0	9
Elective	6	15	21
Fetal indications	5	96	101
Maternal medical disease	4	6	10
Maternal surgical disease	0	3	3
Inertia	3	22	25
Unknown	14	198	212

Obviously some sections had multiple indications

TABLE 5

Fetal Weights of Previous and Present Series				
None Reported	0	0.0%	3	0.4%
Under 1,000 Gm.	0	0.0%	6	0.8%
1,000 - 2,500 Gm.	8	6.0%	42	6.0%
2,500 - 3,000 Gm.	24	18.0%	175	25.0%
3,000 - 3,500 Gm.	43	33.0%	236	33.0%
3,500 - 4,000 Gm.	32	25.0%	129	18.0%
4,000 - 4,500 Gm.	5	4.0%	47	7.0%
4,500 - Over	1	0.7%	18	3.0%
Unknown	17	13.0%	54	7.0%

TABLE 6

FULL TERM PREGNANCIES PRIOR TO THIS ONE

None	10
1	20
2	31
3	315
4	185
5	59
6	39
7	12
8	8
9	2
Unknown	30

deciding factor in the posting time for multiple section.

One must bear in mind that some of the causes of prematurity are independent of any decision on the part of the operator, such as accidental hemorrhage, spontaneous rupture of the membranes, spontaneous inauguration of premature labor and misinterpretation of impending or existing rupture.

However, at this point we must concede that fear of rupture is the predominate influence bearing upon prematurity and, in turn, a certain degree of neonatal mortality.

Fertility Records

Known full-term pregnancies (Table 6) prior to the present one and known premature pregnancies (Table 7) are presented. Credit must still be given to the judgment of the operators who were able to deliver such a majority of full-term babies. Twenty per cent of the 710 patients had at least one premature baby and 11% of the same total had more than one premature baby.

We believe there is still some room to improve that figure of prematurity by a more careful evaluation of the baby's size before operation and that neonatal mortality occurring as a result of prematurity could further be improved by the application of continued improvements in present-day technics.

TABLE 7

TOTAL PREMATURE PREGNANCIES—UNDER 2,500 GM.

None	495
1	96
2	26
3	13
4	5
5	2
6	1
Unknown	74

Twenty per cent of the 710 patients had at least one premature baby.

Eleven per cent of the 710 patients had more than one premature baby.

TABLE 8

TOTAL LIVING CHILDREN

1	4
2	11
3	60
4	221
5	221
6	112
7	40
8	22
9	6
10	3
Over 10	3
Unknown	17

This gives a total of 3,349 children living at the time of this study.

The sum of 3,349 living children at the time of this study (Table 8) is merely an estimation based on the figures at hand. It does not take into consideration the unknowns as well as erroneous reports.

The fetal mortality of the previous babies born is illustrated in table 9. At least 65 of these were associated with vaginal deliveries. The remaining 135, born by section, were not all in the multiple section (four or more) category. Therefore, some were lost at the minus Para IV level and thus cannot be included in the ordinary hazards of multiple section. Later figures will reveal over-all fetal mortality.

The total number of abortions are reported abortions and cannot be a true figure (Table 10). Abortion and its relation to multiple section could comprise material for much study and speculation—both of which are not the purpose of this report.

The evaluation of infertility after section (Table 11) leaves much to be desired, and we wish to emphasize the fact that because this question is being raised we merely submit a few figures we were able to obtain as a result of this inquiry.

TABLE 9

PREVIOUS PERINATAL FETAL MORTALITY

None	494
Premature vaginal delivery	18
Term vaginal delivery	32
Premature section delivery	49
Term section delivery	71
Combination of the above	15 (30+)

This gives a previous perinatal fetal loss of something in excess of 200. At least 65 of these were associated with vaginal deliveries.

TABLE 10

TOTAL NUMBER OF ABORTIONS IN THE SERIES

None	483
1	124
2	40
3	9
4	4
5	3
6	0
7	1
Unknown	47

This gives a total of 269 abortions in the 710.
Twenty-five per cent of the patients had at least one abortion.
Two and four-tenths per cent of the patients might be considered habitual aborters.

Points of Interest in the Previous Obstetric Histories of the Patients Under Study

Some reflection should be made upon the past obstetric experiences of the patients under study.

Point 1: It is obvious that all patients could not have had their sections performed by the same technic. It is questionable in our minds whether this makes for a significant difference in the final outcome of the welfare of the uterus. The judgment, skill and experience of the operator must play an important part in the repair of such uteri. Pedowitz and Schwartz[5] state that technic is probably the most important single factor determining the integrity of the scar. If a uterus is allowed to remain to carry a future pregnancy then one must assume that the scar has been judged to be substantial and that the operative site has been repaired in a satisfactory manner .

Point 2: It would seem that the incidence of preoperative labor is too high even though some of these labors must be attributed to an incidental spontaneous inauguration. It therefore follows that the calculated operative time needs more careful consideration.

TABLE 11

EVALUATION OF POSTSECTION INFERTILITY

None demonstrated	221
Insufficient time	161
Over 40 years of age	7
Para IV plus	22
Subsequent abortions	2
Absolute voluntary	19
Absolute involuntary	19
Unknown	277

The authors wish to emphasize that this phase of the study warrants a much more exhaustive approach than was possible with our present method of collecting data over a nationwide area. In light of the fact that this question has been raised by other authors we submit our statistics as a preliminary report. There were 19 cases of involuntary sterility out of 433 cases reported, an incidence of 4.3%.

Point 3: We cannot conclude, on the basis of these studies, that postoperative morbidity has any great influence upon the later occurrence of defective scars, ruptures or subsequent hysterectomy. We subscribe to the opinion of Pedowitz and Schwartz that an afebrile postoperative course does not guarantee a good scar nor does a febrile course indicate a bad scar.

In the summation of the gestational achievements of all the pregnancies of this group prior to the present pregnancy (Table 12), it is interesting to note that despite the fact that the premature termination of pregnancy resulting in premature babies is a hazard with the multiple section group, the premature termination of pregnancy in the form of abortion outnumbers that of premature delivery *per se*. Could this be, in turn, another hazard?

The Latest Section: Fetal Results

We again emphasize that the risk of prematurity remains rather consistent and seems to be independent of parity. Fetal weights with the last section compare with fetal weights of previous sections (Table 13). This holds true even at the Para II and III levels.

Fetal mortality with the present section as listed is a gross and not a corrected figure (Table 14). Even so it would seem that the

TABLE 12

THE SUMMATION OF THE GESTATIONAL ACHIEVEMENTS OF THIS GROUP

Full term pregnancies	3,134
Premature pregnancies	215
Abortions	289
Involuntary-infertility	19

POINT 1

270 of the patients had all laparotrachelotomies.
140 of the patients had all classical sections.
83 of the patients had a mixture of the two types.
In 217 cases there was inadequate data on all of the sections to classify them.

POINT 2

414 of the patients had some labor with at least one of their sections.
145 of them had no labor with any section.
In 151 cases there was inadequate data on all of the sections to classify them.

POINT 3

With regard to previous postoperative morbidity:
449 patients were known never to have run a morbid course.
26 patients had a history of at least one bout of mild metritis.
2 patients had a history of at least one bout of severe metritis.
22 patients had a history of at least one morbid postoperative course, the cause of the morbidity being something other than metritis.
In 210 cases there is inadequate information.

POINT 4

No attempt is made to record the myriads of anesthetic technics utilized but the authors continue to be amazed at the relative low incidence of local and regional anesthetics with their obvious advantages in this type of surgery.

TABLE 13

WEIGHT OF BABY THIS SECTION

Under 1,000 Gm.	6
1,000-2,500 Gm.	42
2,500-3,000 Gm.	175
3,000-3,500 Gm.	236
3,500-4,000 Gm.	129
4,000-4,500 Gm.	47
4,500 and over	18
Unknown	57
Total	710

TABLE 14

FETAL RESULT—PRESENT SECTION

Lived	653
A. Died before operation	17
B. Died during operation	2
C. Died neonatally	31
Unknown	7
Total	710
Fetal mortality rate	7.00%
Fetal mortality rate previous series	5.38%
Fetal mortality rate for both series	6.70%
Fetal mortality rate for all pregnancies in patients studied	5.70%

over-all risk to the baby in the category of multiple sections is not much greater than that of the section baby at lower levels of parity. Later we shall list fetal losses directly attributable to multiple section.

In a study of the causes of fetal death (Table 15), we must be reminded that babies born in this category are also subject to the ills of babies born by means of other methods of delivery. There will always remain a certain number of defects of the newborn and to this date, a certain number of incurable congenital diseases. For want of more detailed information we feel incapable of correcting the fetal mortality of this series but it certainly is obvious that many losses cannot be attributed to the hazard of even one cesarean section.

The Latest Section: Maternal Results

At this stage of parity in which section is a sure, planned method of delivery, labor should be avoided whenever possible (Table 16). One must also bear in mind the existence of a minority of operators who will await the onset of labor to insure the term maturity of the baby.

TABLE 15

CAUSES OF FETAL DEATH THIS SECTION

None	656
Immaturity	13
Anoxia from causes other than atelectasis	14
Atelectasis with hyaline membrane	7
Atelectasis without hyaline membrane	4
Congenital malformation	6
Other	12

TABLE 16

LABOR THIS SECTION

None	620
Early	64
Medium	11
Late	3
Unknown	12
Total	710

TABLE 17

TYPE OF SECTION

Laparotrachelotomy—no labor	371
Laparotrachelotomy—labor	61
Classical—no labor	156
Cesarean hysterectomy—no labor	54
Cesarean hysterectomy—labor	13
Type unknown (no hysterectomy)	55
Total	710

Positive information with regard to the type of section performed with the last delivery is listed only (Table 17). The remaining cases consisted of those in which no information whatsoever was obtainable.

The general blood loss picture we believe is minimal and merely denotes adequate preparation and treatment of the patient in the operating room (Table 18).

In comparing blood loss with diagnosis and treatment, blood loss is found to be consistent both with the circumstances, complications and operative procedure (Table 18, A). One can usually expect to lose more blood with rupture, hysterectomy and large babies. However, we repeat our original contention that blood loss is extremely variable and seems to have little significance in relation to multiple sections.

A corrected morbidity rate of 7% in all cases is reported (Table 19). There seems to

TABLE 18

HEMORRHAGE THIS DELIVERY

None	259
0- 250 cc.	116
250- 500 cc.	150
500- 750 cc.	45
750-1,000 cc.	7
1,000-1,500 cc.	11
1,500-2,000 cc.	2
Over 2,000 cc.	8
Unknown	112
Total	710

TABLE 18, A

750-1,000 cc.	7	Cases
No lesion, no hysterectomy	4	
Large baby	1	
Dehiscences, no hysterectomy	1	
Total hysterectomy, placenta accreta	1	
1,000-1,500 cc.	11	Cases
No lesion, no hysterectomy	2	
Large baby	2	
Subtotal hysterectomy, placenta accreta	1	
Subtotal hysterectomy, defective scar	2	
Total hysterectomy, defective scar	1	
Subtotal hysterectomy, stony	2	
Subtotal hysterectomy, rupture	1	
1,500-2,000 cc.	2	Cases
Subtotal hysterectomy, "hemorrhage"	1	
Subtotal hysterectomy, rupture	1	
Over 2,000 cc.	7	Cases
Total hysterectomy, rupture	2	
Subtotal hysterectomy, rupture	1	
Rupture, no hysterectomy	1	
Large baby, subtotal hysterectomy	1	
Subtotal hysterectomy, placenta accreta	1	
Subtotal hysterectomy, "hemorrhage"	1	

be little foundation to the belief that infection influences the future of the scar.

Table 20 lists the condition of the mother upon discharge following the present or last section. Certainly a maternal mortality of zero speaks for itself when we are dealing with any obstetric complication and, in the multiple section patient, should always approach that figure to justify continuation of the practice of cesarean section at high parity levels.

The Scar

The evaluation of defective scars by the various operators, as mentioned before, leaves much to be desired in contradistinction to the observation and consequent diagnosis of rupture and dehiscence (Table 21). This is an extremely variable factor in judgment and what seems to be a scar may simply be an area

TABLE 19

POSTPARTUM INFECTION

Afebrile	555
Endometritis	13
Mastitis	2
Thrombophlebitis	5
Infected perineum	0
One day fever	83
Urinary tract infection	7
Infected abdominal wound	6
Septicemia and/or peritonitis	0
Intercurrent disease	6
Fever—cause not described	9
Unknown course	24
Total	710

This gives an uncorrected morbidity rate of 18%. Corrected by definition the morbidity rate is 7%.

TABLE 20

CONDITION OF MOTHER ON DISCHARGE

Good	609
Fair	8
Improved	69
Died	0
Unknown	24
Total	710

of thinned muscle elements such as is commonly seen in the lower uterine segment. We believe the majority of so-called defective scars remain intact enough to carry on another pregnancy as attested by the fact that such a high percentage of cases judged to have defective scar had no hysterectomy and were left alone. Eighty-two per cent of all cases in the second series were considered not to have pathologic scars and 80.6% for the entire series. There was an over-all incidence of 2.1% having had rupture of the uterus and 2.6% having had dehiscence.

At this point we deem it necessary to define the difference between rupture and dehiscence because there are a few observers who use the terms synonymously and yet, from the standpoint of actual pathologic change and fetal survival these two conditions are far apart.

Collected data supplied us for electronic computation revealed a report in these two categories which were irreconcilable, making it necessary because of inconstant terminology to analyze each case report separately. There was an appalling failure to agree upon the difference between the two conditions as well as what constitutes a defective scar. It became necessary, therefore, for us to set a norm which could remain constant throughout this study and which, in turn, could be clearly expressed.

Therefore, in this presentation the term

TABLE 21

SUMMARY OF THE STATUS OF PREVIOUS SCARS AT THIS SECTION

No pathologic scars		582	82.1%
Lacerations of the uterus		16	2.2%
Dehiscence		15	2.1%
Short	6		
Long	4		
Both types	4		
Unknown type	4		
Defective scars		97	13.6%
Thin and narrow	53		
Thin and wide	41		
Unknown type	3		
Both Series			
No pathologic scars		702	80.6%
Ruptures		18	2.1%
Dehiscences		22	2.6%
Defective scars		124	14.7%
Other		1	

rupture of the uterus is used synonymously with laceration of the uterus. This agrees with Eastman's[6] overt rupture but is at variance with the criteria of Pedowitz and Schwartz. On the other hand, we choose to call Eastman's occult rupture—dehiscence. We present both as separate and distinct from defective scar. In this manner alone were we able to report the information supplied us. If, on occasion, it was impossible for us to differentiate, we classified the condition as the more serious lesion. If there was any hint of laceration either clinically or pathologically we so designated it even if the complete course seemed to favor dehiscence.

In a study of mortality as a result of abnormal scars, we again would like to emphasize Cosgrove's contention that rupture of the uterus is not always catastrophic (Table 22). Certainly it was never so for the mother and only 50% for the baby. One additional baby which died did not do so before or during the operation. And fetal mortality as a direct result of dehiscence seems to be minimal if at all. No baby died as the result of a defective scar alone. Once again we remind that this fetal mortality as tabulated is uncorrected.

Fifteen of the 16 ruptured uteri were removed immediately postpartum, indicating a reluctance to take any chances at this parity level (Table 23). One rupture in our first series and one in this series were repaired and the uterus allowed to remain. The latter sustained an elective hysterectomy at a later date. Only one third of the cases with scar dehiscence had hysterectomy. The other two thirds, 10 cases, apparently were repaired satisfactorily.

TABLE 22

MORTALITY AS A RESULT OF ABNORMAL SCARS

Lacerations of the uterus			16
Maternal		0	
Fetal		8	
Died before operation—anoxia from other causes	4		
Died during operation—anoxia from other causes	1		
Died before operation—"rupture"	1		
Died before operation—"other"	1		
Died neonatally—immaturity	1		
Dehiscences			15
Maternal		0	
Fetal		4	
Died before operation—anoxia from other causes	1		
Died neonatally—atelectasis hyaline membrane	1		
Died neonatally—congenital malformation	1		
Died neonatally—cause unknown	1		
Defective scars			97
Maternal		0	
Fetal		5	
Died neonatally—immaturity	1		
Died neonatally—immaturity and congenital defect	1		
Died neonatally—immaturity and anoxia other cause	1		
Died neonatally—cause "other"	1		
Died neonatally—cause unknown	1		

TABLE 23

DEFECTIVE SCARS
FURTHER TREATMENT

I. Lacerations of the uterus			16
A. Puerperal hysterectomy		15	
Clinical diagnosis			
Laceration of the uterus	15		
Pathologic diagnosis			
Laceration of the uterus	4		
Laceration of the uterus and defective scar	4		
Hemorrhagic infiltration	1		
"Other"	2		
Normal uterus	1		
No report	3		
B. Elective hysterectomy		1	
Clinical diagnosis			
Defective scar	1		
Pathologic diagnosis			
No report	1		
II. Dehiscences			15
A. Puerperal hysterectomy		4	
Clinical diagnosis			
Dehiscence	4		
Pathologic diagnosis			
Defective scar	2		
Defective scar and hemorrhagic infiltration	1		
"Other"	1		
B. Elective hysterectomy		1	
Clinical diagnosis			
Defective scar	1		
Pathologic diagnosis			
No report	1		

In the area of defective scars and their treatment, we believe lies the greatest possibility for improvement (Table 23, A). Fear of future rupture we believe is the greatest motivating factor. Improvement in evaluation as to what really constitutes a defective scar and improvement in the preservation of the uterus are desired. The latter occupies the narrow field of the operator's judgment, and it is here where the pathologist often pronounces the removed specimen a "normal uterus." On the other hand, many times the pathologist is in no position to oppose the judgment of the clinician who, on the spot, can observe a fresh organ. One could venture to say that it is the extreme caution of the operator which might have a real bearing upon the absence of a single maternal death in this class of patients.

Examples of variations in judgment and subsequent treatment are provided, for instance, by one hospital reporting 24 multiple sections with only one defective scar followed by hysterectomy, by another reporting 36 cases with only four bad scars needing surgery, by still another having 19 cases, 8 faulty scars all requiring removal of the uterus. Another view-

TABLE 23, A

DEFECTIVE SCARS
FURTHER TREATMENT

Defective scars			97
Puerperal hysterectomy		32	
A. Clinical diagnosis			
Defective scar	25		
Pathologic diagnosis			
Defective scar	14		
Uterine scar	1		
Fibrosis	1		
"Other"	1		
Normal uterus	5		
No report	3		
B. Clinical diagnosis			
Hemorrhage	3		
Pathologic diagnosis			
Defective scar	1		
Placenta accreta	1		
Normal uterus	1		
C. Clinical diagnosis			
Placenta accreta	2		
Pathologic diagnosis			
Placenta accreta	1		
No report	1		
D. Clinical diagnosis			
Fibrosis	1		
Pathologic diagnosis			
Fibrosis	1		
E. Clinical diagnosis			
Infection	1		
Pathologic diagnosis			
Infection	1		

point was provided by the hospital which reported 12 pathologic scars among 32 cases but in which only 3 patients were subject to hysterectomy.

Therefore, we are in no position to condemn but rather mildly suggest that in view of the fact that one fifth of all uteri removed for defective scar were judged to be normal uteri, and considering the fact that pathologists also can and do recognize defective scars there might be some room for improvement in this area.

Furthermore, in this series one should not consider all uteri as being removed for a defective scar alone, because some had accompanying disease which demanded removal, such as hysterectomy in 3 for placenta accreta, in 2 for fibrosis, in 3 for hemorrhage and in one for infection. Therefore uteri removed solely for defective scar number 15 of the total of 97.

With the small number of cases dealing with rupture and dehiscence and their relationship to the previous type operation it is difficult to arrive at any conclusion (Table 24). However, from the figures at hand it appears that the classical type of operation predisposes to these complications more than does the low cervical type.

TABLE 24

LACERATIONS AND DEHISCENCES
PREVIOUS TYPE SECTION

Lacerations		16
Laparotrachelotomy only	2	
Classical only	4	
Mixture of types	4	
Unknown types	6	
Dehiscences		15
Laparotrachelotomy only	2	
Classical only	4	
Mixture of types	3	
Unknown types	6	

Summary and Conclusions

After a lapse of 5 years, a follow-up study of patients having four or more cesarean sections reveals that a group of 710 cases had an amazing similarity to the original group of 130 cases with respect to the average number of sections per patient, the average number of babies per patient, the incidence of rupture of the uterus, dehiscence of postcesarean scar and defective postcesarean scars, hysterectomy, fetal mortality and the general clinical habits of handling such cases on the part of the obstetrician.

The average number of sixth sections showed a precipitous drop causing one to offer factors which could possibly influence this phenomenon. Wider acceptance of the safety of multiple section might increase this level of parity.

Original operative indications fall into generally accepted categories. This is important because there seems to be much agreement with the statement of Ferguson and Reid that the original indication for operation is the most important single factor in the prevention of subsequent rupture of the cesarean scar.

A study of fetal weights in both series indicates that the risk of prematurity of the infant is greater in the patient having multiple sections. However, the risk of rupture either spontaneous or that caused by uterine distention and/or labor must be weighed against the calculated risk of prematurity. In the absence of untoward symptoms referable to the scar, the size of the baby should be the deciding factor in the posting time for operation. Note must be made that the majority of those babies delivered were full term attesting to the good judgment of most operators.

Labor, obviously the cause of some ruptures, was allowed preoperatively too often and should not occur except by accident.

Accumulated data in this report has caused us to suscribe to the opinion that morbidity does not have any great significance upon the later occurrence of defective scars and that an afebrile postoperative course does not guaran-

tee a good scar nor does a febrile course indicate a bad scar.

Fetal loss in the multiple section of high parity is no greater than fetal loss in the section of low parity.

Blood loss seems to have little significance in relation to multiple sections and is usually consistent with circumstance, complications and operative procedure.

The risk of mortality, both maternal and fetal, is not greater in cesarean section in high levels of parity.

The existence of defective scars in such uteri, including ruptures and dehiscences in 710 patients, was catastrophic for only 8 babies (1.12%) and never for the mother.

Hysterectomy was performed for rupture in the majority of cases. It was performed in only one third for dehiscence and for the sole indication of defective scar which seemed to be justified in 15 per cent. Five removed uteri were pronounced normal.

The incidence of hysterectomy in this series was 7.46% compared with 7.69% in the first series again revealing a striking similarity in clinical thinking.

Hysterectomy should be performed in the patient having multiple sections only after the uterus has been carefully judged to be pathologic to the extent that it is either diseased or has been weakened to the extent that it cannot sustain the distention of another pregnancy. The present-day evaluation of the post-cesarean scar leaves room for better clinical judgment.

After a study of a second and larger series of patients with four or more cesarean sections it is necessary to conclude once again that the capabilities and integrity of the uterus in these patients have been underestimated and that the routine practice of sterilization at the time of the second or third section should be abandoned.

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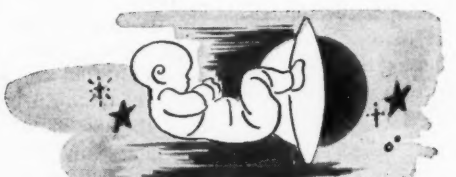

Cesarean Section: A Six Year Review*

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The authors have reviewed the indications for cesarean section and results over a six year period.

SINCE LONG BEFORE MACDUFF was "from his mother's womb untimely ripp'd," the dramatic operation of cesarean section has stimulated both the imagination and the intellect of physicians concerned with obstetric problems. Recent medical progress has permitted liberalization of the indications for abdominal delivery. The increased safety of this convenient method of apparently solving a myriad of clinical problems may have weakened the still sound obstetric principle that the best way for most babies to be born is through the birth canal. The rate of cesarean section which ought to prevail on a given type of service is not an absolutely determinable figure, but depends on many variable circumstances.

Careful study of results obtained by different obstetric departments may be helpful in this regard, especially if the statistics are analyzed critically in the light of a unified departmental philosophy. This presentation, though concerned with over-all statistics from an active teaching service, has as its thesis the necessity for correct indication for the operation, since the authors consider this to be the key to a proper use of abdominal delivery.

Material

This paper presents data on cesarean sections performed in the Department of Obstetrics and Gynecology of Louisville General Hospital from Jan. 1, 1954 through Dec. 31, 1959 (Table 1). During this 6 year period, 16,593 patients were delivered, 343 of them by cesarean section, an over-all incidence of 2 per cent. Louisville General Hospital is charged with the medical care of the indigent population of Louisville and Jefferson County, Kentucky; its Department of Obstetrics and Gynecology is a university teaching service without private patient facilities.

TABLE 1

LOUISVILLE GENERAL HOSPITAL
INCIDENCE OF CESAREAN SECTION

Year	*Patients Delivered*	*Cesarean Sections*	*Section Rate (Per Cent)*
1954	2,777	56	2.0
1955	2,692	45	1.7
1956	2,759	47	1.7
1957	2,725	59	2.2
1958	2,816	69	2.5
1959	2,824	67	2.3
Total	16,593	343	2.0

Indications for Cesarean Section

Table 2 summarizes the indications for the 343 cesarean sections in this series. It will be noted that more than twice as many sections were done because of previous abdominal delivery than for any other indication (45.8% of all operations). Although this figure correctly indicates substantial endorsement of the controversial dictum "once a cesarean section, always a cesarean section," each patient is evaluated individually with respect to age, parity, number and type of previous section, original indication, previous operative and postoperative complications, and type and progress of labor when its onset precedes admission; and occasional previously sectioned patients have been allowed to deliver vaginally, with good results to date.

The most frequent indication for *primary*

TABLE 2

LOUISVILLE GENERAL HOSPITAL
INDICATIONS FOR CESAREAN SECTION IN 343 PATIENTS

Indication	*Number*	*Per Cent*
Previous cesarean section	157	45.8
Cephalopelvic disproportion	78	22.7
Placenta previa	38	11.1
Transverse presentation	20	5.8
Prolapse of the umbilical cord	19	5.5
Abruptio placentae	14	4.1
Other	17	5.0

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abdominal delivery was cephalopelvic disproportion, present in 22.7% of all the cesarean sections, or 41.9% of the *primary* abdominal deliveries. This includes patients with contracted pelvis, excessively large baby, and hydrocephalic fetuses, as well as patients with borderline pelvic measurements failing to progress after adequate trial of labor, women with infants in abnormal presentation, and primigravidas with infants in breech presentation and low normal or borderline pelvic measurements in whom external cephalic version near term had proved unsuccessful. All but 2 of the 78 patients in this group were subjected to preliminary trial of the forces of labor; 58 of the 78 were primigravidas.

The third most common indication, placenta previa, deserves comment. Our only absolute indication for section in this complication is central placenta previa as diagnosed by direct digital palpation; other forms of placenta previa are managed vaginally, by rupture of the membranes with or without scalp traction, unless these simple measures fail to control bleeding. In such event, the indication for cesarean section is predominantly maternal, while with central implantation the indication is chiefly fetal.

Most patients with prolapse of the umbilical cord were first seen after the accident had resulted in death of the infant, so that cesarean section was indicated in only 19 instances. Eighteen babies were born alive, and all but one of these survived. One baby was stillborn.

Premature separation of the normally implanted placenta was the indication for operation in 14 patients, all of whom continued to bleed despite rupture of the membranes with or without stimulation with oxytocin (Pitocin). These operations were done on maternal rather than fetal indication; in no instance was cesarean section performed for so-called "fetal distress" alone.

The 20 patients sectioned for transverse presentation require no special comment. In the remaining 17 patients, the indications for abdominal delivery included ruptured membranes and failed induction of labor in 3 women, amnionitis and failed induction of obligation in 2 patients, obstruction of the birth canal by uterine leiomyomas in 2 instances, uncontrolled preeclampsia with failed induction of obligation in 2 cases, and one example of each of the following: failed induction of obligation in a diabetic patient, soft tissue dystocia due to annular cicatrix of the cervix produced by chronic use of lye vaginal douches, controlled eclamptic toxemia with a cervix unfavorable for induction of labor, previous abdominal pregnancy delivered by laparotomy, dermoid cyst obstructing the birth canal, automobile accident producing fatal injuries, asymmetrical pelvis in a patient with a childhood history of severe poliomyelitis, and anticipated soft tissue dystocia in a patient with an exophytic carcinoma of the cervix.

Type of Operation

The types of cesarean operation employed in this series are summarized in table 3. The transverse low cervical incision was employed most commonly. The classical incision, performed 20 times, was reserved for patients in whom some technical impediment such as broad ligament varicosities contraindicated the low cervical incision. The one extraperitoneal section was done as a demonstration of the technic by a specially qualified member of the attending staff; this approach is no longer routinely taught to residents in this Department. The indications for cesarean hysterectomy were varied, but it should be stressed that desire for sterilization was never a primary indication. If sterilization is to be done in candidates for cesarean section, our preferred method is bilateral tubal ligation following laparotrachelotomy.

In 9 patients, a "T"-shaped incision was made in the uterus. This consisted of a transverse low cervical incision extended vertically in the midline. Six such incisions were employed for the delivery of infants from transverse presentation because it had become ap-

TABLE 3

LOUISVILLE GENERAL HOSPITAL
TYPE OF CESAREAN SECTION

Type	*Number*	
Low cervical	305	
Transverse		275
Vertical		20
Undetermined		10
Classical	20	
Cesarean hysterectomy	8	
Extraperitoneal	1	
"T"-Incision	9	

parent during the extraction that the lower uterine segment incision was about to tear laterally. These experiences have led to a policy of using a vertical low cervical incision in all instances of section for transverse presentation. Such incisions can easily be extended vertically whenever necessary, avoiding the hazard of possible lateral extension into the large para-uterine vessels.

Type of Anesthesia

Table 4 lists the type of anesthesia used for the cesarean sections reported. In 261 of the 343 operations, some form of spinal anesthesia was given, usually tetracaine. Hemorrhagic complications were considered relative contraindications to intrathecal anesthesia; thus, in the 38 patients with placenta previa, cyclopropane was used 17 times, and supplemented local and general anesthesia were used once each. In the remaining 19 women, absence of critical hemorrhagic emergency permitted the use of spinal anesthesia. In the 14 patients with abruptio placentae cyclopropane was the anesthesia selected in 9 instances, spinal anesthesia was used 3 times, and thiopental sodium once. One patient was *in extremis* when first seen, and only oxygen was administered.

Maternal Mortality

There were 2 maternal deaths in this series, each of which resulted from an automobile accident. The first patient, referred to above, was admitted to the hospital in profound shock and suffered a cardiac arrest while lacerations about the face were being sutured. She was temporarily revived by cardiac massage, and emergency laparotomy was done. She had sustained severe abdominal injuries resulting in total separation of the placenta, and a dead fetus was delivered from the contused uterus. The hemorrhagic shock proved to be irreversible and the patient died on the operating table. The other patient who died sustained widespread internal injuries in a catastrophic automobile accident. At laparotomy there was rupture of both liver and spleen, together with extensive retroperitoneal hemorrhage. Since these were the only 2 maternal deaths, it is literally correct to say that, in our experience, the principal cause of maternal death following cesarean section is injury sustained in automobile accidents.

TABLE 4

LOUISVILLE GENERAL HOSPITAL
TYPE OF ANESTHESIA IN 343 CESAREAN SECTIONS

Type	*Number*
Spinal	261
Cyclopropane	65
Thiopental sodium	5
Local (supplemented)	5
GOE	3
Caudal	1
Ether	1
Oxygen	1
Nitrous oxide and oxygen	1
	343

Elective Versus Emergency Section

Elective cesarean section is defined on our service as an operation scheduled in advance for a regular operating hour, and actually performed at that time. All other cesarean sections are defined as emergency operations. Classified in this way, 243 of the operations reported were emergency sections, the remaining 100 being elective. Ninety-eight of the 100 babies born by elective cesarean section were term sized. One of the 2 premature infants weighed 3 pounds 6 ounces, and was delivered following failed induction of obligation in a patient with controlled eclampsia; the other premature infant weighed 5 pounds 5 ounces, and was delivered from a patient scheduled for elective repeat section, so that this case represented an error in judgment involving incorrect estimation of the size of the baby. Fortunately, this baby survived.

Fetal Survival

Table 5 indicates the over-all fetal survival in the 343 cesarean sections in this series. Of the 345 infants delivered, 328 were born alive (95%), while 17 were stillborn. The indications for operation in the 10 term sized stillborn infants were as follows: abruptio placentae with uncontrollable hemorrhage (6 cases), and one case each of placenta previa, fatal automobile injuries, ruptured uterus and cephalopelvic disproportion. In the 7 premature stillbirths, the indications were ab-

TABLE 5

LOUISVILLE GENERAL HOSPITAL
FETAL SURVIVAL IN 343 CESAREAN SECTIONS

Infants delivered		345
Alive	328	
Stillborn	17	
Term (2,500 Gm.+) 10		
Premature (1,000-2,500 Gm.) 7		

TABLE 6

LOUISVILLE GENERAL HOSPITAL
FETAL SURVIVAL IN 16,224 LIVE VAGINAL BIRTHS

	Born Alive	*Died*	*Survival (Per Cent)*
Term (2,500 Gm.+)	14,004	49	99.7
Premature (1,000-2,500 Gm.)	2,029	209	89.7
Immature (500-1,000 Gm.)	191	186	2.6

ruptio placentae in 5 instances and placenta previa in two.

Comparative statistics for fetal survival in 16,224 live vaginal births and the 328 live births by cesarean section occurring in the 6 year period covered are presented in tables 6 and 7. All but one of the 52 premature infants born alive by cesarean section were so delivered on emergency indications, with the single exception already referred to above.

The 8 term sized infants who died neonatally included 2 infants with septicemia, one each with congenital atelectasis, viral hepatitis and pneumonitis following infected labor, and 3 in whom the cause of death could not be determined. The 2 immature fetuses were twins delivered abdominally because of maternal hemorrhage from severe partial placenta previa.

A comparison of the birth weights of infants born vaginally and by cesarean section appears on table 8. The slight increase in the percentage of premature infants delivered abdominally over the number delivered vaginally represents emergency rather than elective indications in all but the one case already mentioned.

Discussion

This analysis of our experience with cesarean section is presented primarily to emphasize the importance of rigorous application of principles governing indications for cesarean section. These indications may be principally maternal or principally fetal. A *maternal* indication is present when the section is done to avoid serious consequences to

TABLE 7

LOUISVILLE GENERAL HOSPITAL
FETAL SURVIVAL IN 328 LIVE BIRTHS BY CESAREAN SECTION

	Born Alive	*Died*	*Survival (Per Cent)*
Term (2,500 Gm.+)	274	8	97.0
Premature (1,000-2,500 Gm.)	52	12	76.9
Immature (500-1,000 Gm.)	2	2	0.0

TABLE 8

LOUISVILLE GENERAL HOSPITAL
CLASSIFICATION OF 16,552 LIVE BIRTHS BY WEIGHT

	Vaginal (16,244 Births)	*Cesarean Section (328 Births)*
Term (2,500 Gm.+)	14,004 (86.3%)	274 (83.5%)
Premature (1,000-2,500 Gm.)	2,029 (12.5%)	52 (15.9%)
Immature (500-1,000 Gm.)	191 (1.2%)	2 (0.6%)

the mother, regardless of fetal hazard. A *fetal* indication motivates cesarean section when the mother might be delivered vaginally without undue danger, but only at the expense of increased risk to the fetus. Classified in this way, the predominantly maternal indications in this series were previous cesarean section, severe partial placenta previa, abruptio placentae, and failed induction of obligation. The predominantly fetal indications were cephalopelvic disproportion, transverse presentation, central placenta previa, and prolapse of the umbilical cord.

Perhaps the most controversial of the common indications for abdominal delivery is previous cesarean section. The decision to permit vaginal delivery in a patient with a previous cesarean delivery should depend on several considerations. The history of the postoperative recovery from the previous operation should be known. If the puerperium following the original section was stormy and febrile, one can assume that the scar in the uterus is sizeable, a circumstance which increases the hazard of uterine rupture. If the indication for the previous operation is nonrecurrent, delivery from below may be justifiable in selected cases, but only if the responsible physician is in constant attendance throughout the labor to protect the patient from the serious consequences of possible uterine rupture.

We believe that most patients with premature separation of the normally implanted placenta can be delivered vaginally, since rupture of the membranes and oxytocic stimulation usually suffice to control hemorrhage. However, when these simple measures do not bring about hemostasis, cesarean section may be indicated on a purely maternal basis; and occasionally it may be necessary to perform abdominal delivery even though the baby is known to be dead. So-called "fetal distress," as evidenced by irregularities in the fetal heartbeat or meconium in the amniotic fluid,

is an unreliable index of the condition of the baby, and ought not to motivate abdominal delivery in the absence of some other more definite indication.

When there is an urgent maternal indication for the induction of labor, there is a possibility that the usual methods of induction may fail to put the patient into labor because of failure of the uterus to react to oxytocin. Examples of such inductions of obligation would include women with severe preeclampsia who have not responded to medical treatment, some patients with severe hypertensive cardiovascular disease, and diabetic women at about the 38th week of gestation. Since the indication for termination of pregnancy persists in these cases even when the induction has failed, and since the dangers of amnionitis and other superimposed complications increase rather than diminish with delay in securing delivery, it is justifiable to perform abdominal delivery promptly in any patient failing to respond to such an induction procedure.

Finally, the purely fetal indication of prolapsed umbilical cord rarely applies, since section is indicated only when the prolapse occurs in the hospital where immediate operation can be done. Unfortunately, most such cases are not seen by the physician until the baby is either dead or seriously compromised, and in this event cesarean section is futile and should not be contemplated.

Summary and Conclusions

1. Data are presented from 343 cesarean sections performed at the Louisville General Hospital during the 6 year period from Jan. 1, 1954 through Dec. 31, 1959.

2. These cases are analyzed with respect to maternal and fetal survival, type of anesthesia, type of cesarean section, and principles guiding the choice of patients for abdominal delivery.

3. The importance of establishing clear-cut maternal and fetal indications for cesarean section is stressed.

Good health and good sense are two of life's greatest blessings.
—Publilius Syrus (Circa 42 B.C.) Translation by Darius Lyman.

A Ten Year Experience with Cesarean Section in a 50 Bed Hospital*

B. C. CHATHAM, M.D., *Chickasha, Okla.*

By contrast to the two preceding papers, this one makes comparisons by considering the experiences of a small community hospital in the area of cesarean section.

IN AUGUST 1959 the Chickasha Hospital, a 50 bed proprietary general hospital, closed after some 50 years service to allow the opening of a new County Hospital. The hospital had been accredited by the Joint Commission for the last 10 years of operation. Inasmuch as this was a small hospital in a rural area, it was felt worthwhile to analyze the cesarean sections for the period of Jan. 1, 1949, through Dec. 31, 1958. It was hoped the experience might compare favorably with that of general hospitals in the metropolitan areas. To the medical profession in the metropolitan area, this may not seem too important. However, the physician of a rural area will understand, since too often our patients leave us to consult the "specialist" in the city. If we can show our results are as good, we may hope these "medical nomads" will remain under our care.

More important, however, is the need to encourage both young generalists and specialists to settle in communities such as ours. We sincerely believe we can offer a good medical association to these men as well as a fine community in which to live and raise a family. We really believe medicine can be practiced well in small communities because the physician knows his patients better than does the physician of the metropolitan area.

Table 1 shows the incidence, by year, of sections and attendant maternal and fetal mortality. These operations were done by 4 operators; I did slightly less than 50% of them.

There were no maternal deaths. Two mothers left the hospital without babies: (1) a very premature infant in a case of placenta praevia centralis, (2) a stillborn infant from massive abruption of the placenta (the infant was dead before operation).

TABLE 1

Year	*No. Deliveries*	*Number of Sections*	*% Sections Average*	*Maternal Death*	*Fetal Death*
1949	260	8	3.0	0	1
1950	244	11	4.5	0	0
1951	256	8	3.1	0	0
1952	279	5	1.7	0	1
1953	257	8	3.1	0	0
1954	282	6	2.1	0	0
1955	329	9	2.7	0	0
1956	338	3	0.8	0	0
1957	369	7	1.8	0	0
1958	309	7	2.5	0	0
Total	2,923	72	2.5%	0	2

Table 2 shows the maternal morbidity and the number of cases each year receiving and not receiving antibiotics in the puerperium. These figures are revealing since they show that section carries a very high morbidity rate, albeit a zero mortality rate. If our antibiotics become less effective, we again may be doing more difficult vaginal deliveries in preference to cesarean sections.

Before reviewing these figures, I had thought we had been brave in our use of antibiotics (this includes sulfonamides as well as antibiotics), but I found to my dissatisfaction that we used these drugs very liberally, and I now wonder if they were as necessary as we thought at the time. This much can, however, be said—we

TABLE 2

Year	*Maternal Morbidity*	*Antibiotics Used*	*No Antibiotics Used*
1949	1 in 8 cases	5	3
1950	2 in 11 cases	7	3
1951	2 in 8 cases	7	1
1952	2 in 5 cases	5	0
1953	0 in 8 cases	6	2
1954	3 in 6 cases	3	3
1955	0 in 9 cases	5	4
1956	0 in 3 cases	0	3
1957	0 in 7 cases	1	6
1958	2 in 7 cases	4	3

*Read before the Section on Obstetrics, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

did not use these drugs prophylactically—they were all given on specific indication.

Table 3 shows the type of section done and the number of patients receiving blood transfusions.

The classical sections were done for two reasons: (1) in the presence of placenta praevia and, (2) when fast action was indicated—as in abruption of the placenta or in fetal distress. Transfusions were given only on these indications: (1) bleeding of severe nature with shock, and (2) hemoglobin levels of below 10 Gm. per 100 ml. No transfusions were used as "tonics," and there were no transfusion reactions other than slight "pyrogenic reactions."

Table 4 shows the type of anesthetic used. We feel very strongly about not using general anesthesia and so strong is our belief that we will not do a section under general anesthesia if we expect a live baby. There has been no more serious untoward reaction from spinal than headache, nor have there been problems with local anesthesia. In using either local or spinal anesthesia, thiopental is added after the cord has been clamped for an easier closure following emptying and suturing of the uterus.

Table 5 shows the incidence of primary and subsequent sections.

Our thought has been and continues that, "once a section, always a section" is best for our small hospital. We believe women can be delivered vaginally after section if facilities are immediately available for section during the trial labor. Our emergency surgical set-up requires about one hour's notice. We believe an hour might mean the difference between a live baby or a live mother if the uterus should rupture during this trial of labor.

The reasons for our first sections reflect clearly our philosophy about cesarean sections:

TABLE 3

Year	*Classical*	*Low Segment*	*Transfusion*
1949	2	6	2
1950	0	11	1
1951	0	8	2
1952	0	5	4
1953	2	6	2
1954	1	5	1
1955	2	7	3
1956	1	2	0
1957	0	7	2
1958	1	6	2
Total	9	63	19

TABLE 4

Year	*Local*	*Spinal*	*General*
1949	2	6	0
1950	0	11	0
1951	0	8	0
1952	3	2	0
1953	1	7	0
1954	1	5	0
1955	0	9	0
1956	1	2	0
1957	1	6	0
1958	1	6	0
Total	10	62	0

1949: (1) Placenta praevia
(2) Cephalopelvic disproportion—trial labor

1950: (1) Diabetic mother
(2) Abruption of placenta
(3) Cephalopelvic disproportion—trial labor; first delivery vaginal with spastic child
(4) Cephalopelvic disproportion—trial labor
(5) Cephalopelvic disproportion—difficult first delivery, stillborn infant
(6) Placenta praevia

1951: (1) Uterine inertia
(2) Difficult first delivery—stillborn child
(3) Prolapse cord, breech, 5 cm. dilatation
(4) Placenta praevia
(5) Age 43, breech, first pregnancy—infant weighed 9 lbs.

1952: (1) Severe preeclamptic; unresponsive to treatment
(2) Severe abruption of the placenta

1953: (1) Cephalopelvic disproportion; difficult first delivery, stillborn child
(2) Severe preeclampsia; failed medical induction
(3) "Past 40"—no children living
(4) Prolapse cord—not in labor
(5) Abruption of placenta

1954: (1) Cephalopelvic disproportion; trial labor
(2) Cephalopelvic disproportion; trial labor
(3) Prolapse of cord—not in labor
(4) Uterine inertia

1955: (1) Placenta praevia
(2) Questionable disproportion; questionable inertia
(3) Diabetic mother

1956: (1) No primary sections

TABLE 5

Year	*Primary*	*Repeat*
1949	2	6
1950	6	5
1951	5	3
1952	2	3
1953	5	3
1954	4	2
1955	3	6
1956	0	3
1957	1	6
1958	2	5

1957: (1) Transverse lie; back over inlet—in labor
1958: (1) Placenta praevia and abruption; spastic infant
(2) Past 40—first pregnancy, schizophrenia, antropoid pelvis

A few interesting sidelights were revealed by the above figures: All patients were white (we do have negro patients); 3 hysterectomies were done: (a) one for fibroids, (b) 2 for ruptured uterus unsuitable for suture.

3 associated appendectomies—no unusual course postoperatively
30 had tubal ligations (Pomeroy)
Shortest stay—5 days
Longest stay—13 days
Average stay—8.4 days
Youngest patient—age 17
Oldest patient—age 43
Average age—27.8 years
Complications:
Most frequent—urinary tract infections
Most serious—ileus requiring suction
No wound disruptions
No emboli
No thrombophlebitis

During 1959 we had our first maternal death associated with cesarean section, and the autopsy revealed such an unusual finding that brief review here seemed justified:

A 36 year old white gravida IV, Para II, abortus I was seen during the first trimester of her 4th pregnancy. Her first pregnancy terminated in an uncomplicated vaginal delivery of a viable infant, while the second pregnancy ended in a spontaneous abortion requiring dilatation and curettage. The third pregnancy was terminated by cesarean section for placenta praevia with a viable infant.

The last menses began on Feb. 9, 1959, and term was calculated for Nov. 16, 1959. The history and physical examination were not remarkable except for a uterine pregnancy which progressed without complication to November 5, when she was admitted to Grady Memorial Hospital for an elective repeat section to be done on November 6. Initial laboratory work consisted of a chest x-ray which revealed no abnormalities; a negative serologic test for syphilis; hematocrit of 40%, Type O, Rh positive. Numerous urinalyses were within normal limits. B.P. was never above 110/70.

On November 6, under a controlled, satisfactory spinal anesthesia, a laparotrachelotomy was done without incident. A viable infant was obtained. Blood loss was not excessive and transfusion was not used. On completion of the procedure she was sent to the recovery room for 45 minutes, where her B.P. was stable at 100/60 to 110/70. She had reacted well by 10 a.m. and was taken to the obstetric ward.

At approximately 10:30 a.m. she sat upright in bed and complained of being "short of breath." The family summoned the floor nurse, who found the patient pulseless and without demonstrable blood pressure. Artificial respiration, intravenous stimulants, and fluids were given by the attending physician and anesthetist, all to no avail. Cardiac massage was not attempted.

At autopsy the abdomen contained 2,000 to 3,000 cc. of blood. The uterine incision was dry and intact. However, at the left cornu of the uterus on the posterior uterine surface, in the region of the utero-ovarian ligament, there was found a ruptured varicosity of 1 to 1.5 cm. in diameter. The remainder of the autopsy was remarkable in that no other significant disease was found.

The pathologist, after detailed study of the specimen and the medical literature, attributed the death to exanguinating hemorrhage from a ruptured utero-ovarian vein.

Comment. Having operated on the patient and then having seen the size of the ruptured varix, I am certain that no amount of heroic action would have allowed this woman to be prepared and re-operated. Much more blood would have run out of the ruptured varix than could possibly have been poured into her. She was a victim of fate—had this rupture occurred between the leaves of the broad ligament rather than into the peritoneal cavity, tamponade by the broad ligament would have allowed gradual blood loss by hematoma formation and remedial measures could have been instituted.

Similar cases have been reported in the medical literature. The bibliography reveals fewer than 100 previously reported cases of ruptured utero-ovarian vein as a complication of pregnancy and the puerperium.

Summary

Experience of a 50 bed community hospital with cesarean section is reported. A rare, fatal complication of pregnancy is reported in detail. Draw your own conclusions.

Discussion of the Papers on Cesarean Section By Drs. McNally, Haynes and Chatham

Dr. Silas H. Starr, Louisville, Ky. Discussion of cesarean section may be likened to religion and politics. Each person has his own ideas and many times it is impossible to influence his opinions. This is the third meeting I have attended within 2 months where several presentations on cesarean section were given, and now I feel fairly well saturated with the subject. Various facets are quite controversial, but two of the three papers given here have followed an orthodox pattern. The paper by Dr. McNally is concerned with one small part of the vast subject of cesarean sections, and I shall allude to his paper later.

Dr. Chatham's presentation was interesting and enlightening. It is stimulating to receive such a report from one of the districts removed from the medical centers. The series is necessarily small, but with the data at hand, I can find only agreement as far as indications and the excellent end results are concerned.

In this paper, however, Dr. Chatham stresses that antibiotics are employed only as therapeutic agents and not for prophylaxis, but in his tabulated results he lists only 12 cases of morbidity whereas antibiotics were given on 43 occasions.

It is our usual practice to use antibiotics only when infection is present. We employ, as he does, the lower segment operation almost exclusively. I am not as adamant concerning a general anesthetic as he is. In fact, our usual routine is to use a spinal anesthetic, and to give enough Pentothal Sodium to keep the patient asleep. We do not hesitate to give usual preoperative drugs of promethazine HCl, meperidine HCl, and hyoscine, either. When expecting a premature baby we are not so liberal with a general anesthetic. It is certainly agreeable to note that the patients operated upon because of cephalopelvic disproportion were given a trial labor. It is surprising how often such possible sections will deliver vaginally successfully if allowed a chance to do so.

Dr. Haynes as usual has given us a masterful and scholarly presentation. His over-all incidence of 2% cesareans is comparable to Dr. Chatham's 2.5 per cent. The indications listed are fairly well standardized, and except for extremists, I do not believe there will be any disagreement. It is extremely gratifying to me that Dr. Haynes has liberalized to some extent the indication of previous cesarean section. In most series of cases, including my own, usual subsequent cesareans follow the initial one, but by no means is this a hard and fast rule. Especially in a patient who has achieved a successful vaginal delivery before her cesarean, subsequent vaginal deliveries may be readily accomplished. At the risk of triteness, I must emphasize the need for individualization.

Dr. McNally has presented a barrage of tables and an interesting discussion of 840 patients subjected—if I may express it thus—to 4 or more cesarean sections. The paper is interesting and most worthwhile, but requires much study to digest and absorb all the data and discussion involved. I congratulate him on his painstaking study, and his work does much to refute the idea that patients should be sterilized usually after a second, and almost always after a third cesarean section. Such an idea probably was lifesaving to many patients in an earlier era, but at the present time most of us with better technic do not believe such a necessity exists. In fact, many patients to my knowledge, have been sterilized at their urgent request after a third section, rather than because it was necessarily indicated medically. The fact that only those qualified to perform the operation do so in the vast majority of cases at the present time in itself will render repeat pregnancies much less dangerous. The low segment operation is almost always thought to preserve the integrity of the uterus much better than the classical approach.

I would take issue with Dr. McNally on one point, however. Repeat elective cesareans have had repeated criticism in regard to the birth of a much higher proportion of premature babies. He condones this as a calculated risk vis-á-vis a possible ruptured uterus if pregnancy continues beyond a certain unspecified time in certain unspecified cases. If such a course is justifiable then I believe the risks involved for the mother are too great to permit another pregnancy.

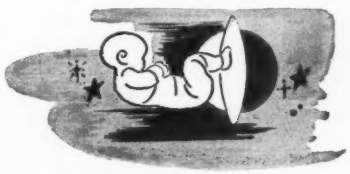
Eastman defines a grand multipara as a woman with her 7th viable pregnancy and notes enough expected complications in such a so-called normal case, that he considers sterilization a justification on multiparity alone. How then, except in the exceptional case, can one condone an unlimited number of insults to the uterus with incisions into it repeatedly?

Although this is not completely relevant to the present discussion, Riva has collected a series of 238 cases with postcesarean pregnancies and 75% of these were delivered per vaginam. Perhaps Dr. McNally is simply using as his thesis the fact that many sections may be performed on one patient but it is well to point out that if so many pregnancies will follow a cesarean, perhaps a great many of his series should have been managed by labor and delivery from below.

Another question that must be raised is, when does the uterus rupture—before term, or in labor? Personally I am more placid in handling the patient who had a low segment operation by a skilled operator then one who had a classical operation. Statistics are quite one sided on this score, also.

I must emphasize one more statement by Dr. McNally and concurred in by most obstetricians. Perform the first cesarean only on strict indications. Far too many times we are confronted with a pregnancy after a cesarean which may easily have been a patient with a normal obstetric history. In that way we may avoid some of the concern over a potential uterine rupture.

It has been a pleasure to read these three papers and to comment on them. Cesarean section and its many facets could be discussed for the remainder of the day and let me not be the one to attempt to cover all the points in this much too long discussion.



Untreated Hypertension*

RAYMOND D. PRUITT, M.D.,† *Houston, Tex.*

This review should be of great value to the physician interested in and treating hypertension. What is the natural course of the disease? This question must be in mind as he embarks on treatment. What is he to anticipate from treatment in long-term results? How will this be related to the course of the disease? And what of the pathogenesis and course of hypertension as related to onset in the fourth decade or the sixth decade? This review may be read with great profit as the treatment of hypertension is undertaken.

THE SUBJECT "Untreated Hypertension" affords basis for sober reflection. The advent of drugs of real therapeutic effectiveness has served to enforce on thoughtful physicians the need for exact data concerning the course of untreated hypertensive disease if precise appraisal is to be made of the good or ill attending present-day pharmacologic or surgical methods of treatment. It may seem strange that the many years of therapeutic frustration which attended the use of ineffective medications have not left as their heritage an abundant evidence on the natural history of hypertensive disease. But as Leishman[1] has observed of the admirable studies of untreated hypertension available today, "it is doubtful if any of these can be regarded as fully satisfying the requirement (i.e., of supplying a satisfactory yardstick against which the long-term success of modern hypertensive care can be measured) since they suffer in common the disadvantage of all retrospective studies that the picture presented is insufficiently detailed."

Realization that each advance in therapy will increase the moral imperative for treating every patient afflicted with hypertensive disease has been attended by determined efforts by certain thoughtful clinicians to define the natural history of untreated hypertensive disease. The frustrating experiences which attend such efforts have been editorialized upon by Dr. George Perera[2] who summated his multiple annoyances in the phrase, "The Unnatural History of Hypertensive Disease." He observed that the natural history not only of hypertension but of many other diseases as well, has been rendered difficult of definition because, "in this day and age, the usual turnpikes traversed by patients have become obscured by a smog of therapies which slows the progress of the ill and hides the view."

What is Hypertension?

In the course of every well-organized symposium on hypertension, some time, and usually a considerable amount of it, is spent in deciding what is and what is not hypertension. Sir George Pickering, as best I can comprehend his delightfully developed arguments, concludes that a precise distinction between normal blood pressure and high blood pressure is as impossible of definition as an arbitrary division between people of normal height and people who are to be called "tall." Unfortunately, the biologic consequences of a markedly elevated blood pressure are of much greater significance and concern both to the patient so afflicted and to his physician, than are the biologic consequences of being remarkably tall. And so with the uneasy conscience of one who desecrates truth on grounds of enforced expediency, a definition of hypertension is here recorded in order that we may share at least in a common point of departure. "Hypertension is . . . defined as the repeated finding of a casual diastolic pressure of 90 mm. of mercury or more after exclusion of those with transient rises in blood pressure, those with marked obesity (unless repeated values are in excess of 105), and those with possible arteriosclerotic causes (unless repeated values are in excess of 100)." This definition as proposed by Perera[3] must be placed in context with his definition of hypertensive vascular disease (primary or essential hypertension), "as a disorder characterized by the presence of hypertension when it is not secondary to a known primary pathologic process."

*Presented before the 25th Annual Meeting of the Texas Heart Association, Sept. 9-10, 1960, Dallas, Tex.

†From the Department of Medicine, Baylor University College of Medicine, Texas Medical Center, Houston, Tex.

Hypertension secondary to a known primary pathologic process poses a different problem as regards cause and treatment from primary or essential hypertension. In this discussion of untreated hypertension only the primary variety of the disease will be considered.

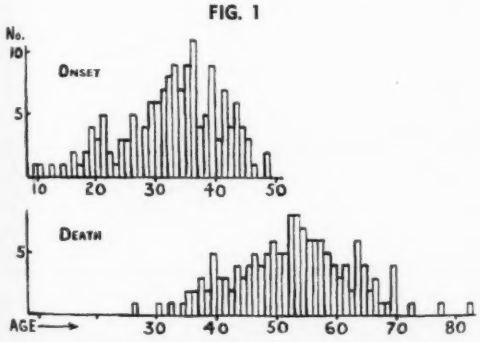
The Pattern of Untreated Hypertensive Vascular Disease

I. *Onset of the disease and duration of the disease until death of patient from the disease.*

Something of the difficulties which attend definition of the pattern of untreated chronic disease will be identified by reflecting on how many patients are observed by an individual physician over a time sufficient to include a period before hypertension developed, the entirety of their surviving years after hypertension developed, to the termination of their life by a cause related to hypertension. A series of 150 such patients who received their medical care at the Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, has been described by Perera.[3] In figure 1 is reproduced a chart from his report. Among the points of interest reflected in this chart are the following:

(1) Between the ages of 9 years and 37 years, the number of individuals exhibiting for the first time elevation of blood pressure to hypertensive levels increased quite steadily. From 37 years to 49 years the incidence of new cases declined in a curve somewhat more abrupt than was the ascending limb. Perhaps the most striking fact is the sharp termination of the series at the age level of 50 years. An arbitrary factor contributed to this abrupt descent to base line, inasmuch as patients above 50 years of age were not regarded as suitable for introduction into the series unless their diastolic pressures were in excess of 100, a level 10 mm. higher than was acceptable at ages less than 50 years. However, the author adds this interesting comment: "In the experience of this clinic to date, whenever the documented onset of hypertension occurred after the age of 50, a secondary cause for an elevated blood pressure has been discovered." This observation conveys significant implications as regards both the pathogenesis and the treatment of primary hypertension.

FIG. 1



Age at onset and age at death of the same 150 patients with hypertensive vascular disease. (Reproduced with permission of the publisher and the author from Perera[3] in J. Chron. Dis. 1:33, 1955.)

(a) As regards pathogenesis of hypertension, the absence of new cases after the age of 50 years suggests that the disease cannot be a simple expression of cellular aging. The increasingly rapid cumulation of cases prior to age 37 years, reflects the participation of a temporal factor in the development of the hypertensive state. The susceptible individual must live a certain minimum period of years before he becomes hypertensive; but the nonsusceptible individual will not develop essential hypertension however long he may live. In these generalizations, an arbitrary element participates in the same manner and extent as that element participated in the definition of hypertension, but not more so.

(b) As regards treatment of hypertension, the absence of new cases of the essential form of the disease after the age of 50 years places squarely before the clinician his responsibility to search avidly for a pathologic process known to produce secondary hypertension when he encounters significantly elevated pressure readings initially in a patient who is in his sixth or seventh decade of life.

(2) The data included in figure 1 reveal also that when followed from onset of their disease until death, the average patient with essential hypertension lived for approximately 20 years. Three of the 150 patients lived longer than 40 years after developing the hypertensive state. Perera notes that the average patient spent three quarters of his life in the uncomplicated phase of the disease. "Approximately one third of the patients were without symptoms throughout this period, and in three fourths of those with symptoms (that is, fatigue, nervousness, dizziness, palpitation, insomnia, headaches, and so forth), the com-

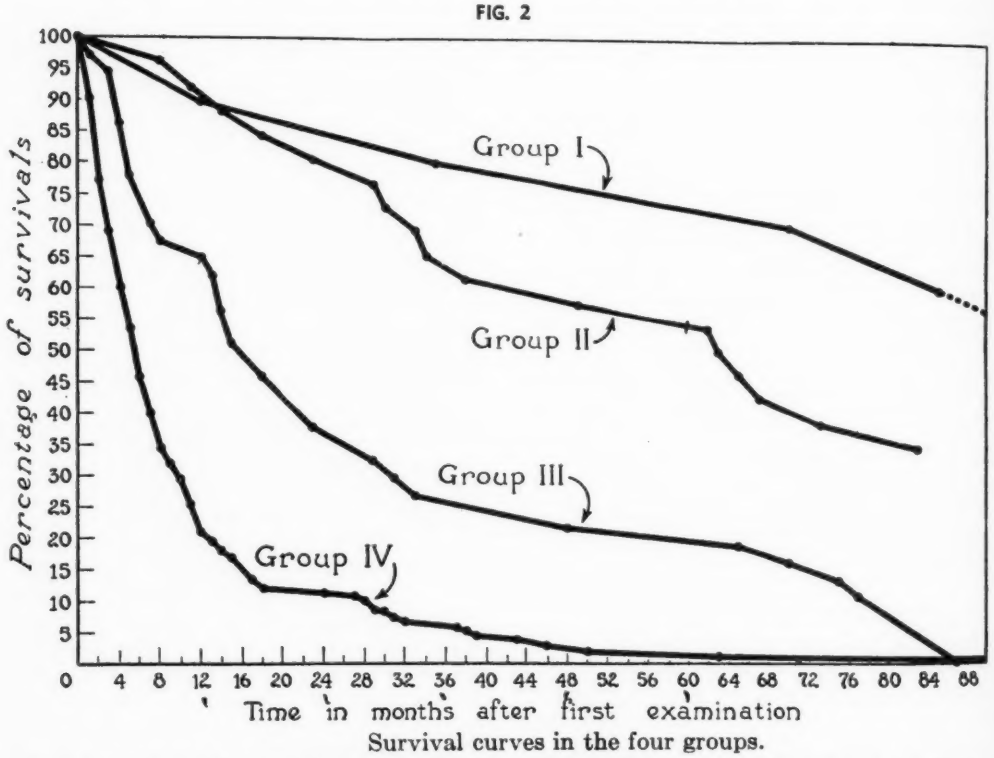
plaints were inconstant or disappeared without specific measures."

(3) The lower division of the chart in figure 1 reveals the remarkable range of ages at which death occurs in patients with hypertension: from 26 years to 82 years. More significant, however, is the concentration of cases dying between the ages of 50 and 60 years. This hump is, to be sure, a correlate to that found in the decade between 30 and 40 years in the age of onset curve. One may deduce that a random series of necropsies would show a decline in the incidence of essential hypertension and its complications as a primary cause of death, but at precisely what age this decline would begin cannot be computed without having a figure for the total number of individuals dying of all causes at each given age. In contrast, the curve defining the severity of coronary sclerosis encountered at necropsy and inferentially as a cause of death reaches a peak at 55 years in men whereafter it forms a plateau extending to 85 years.[4] This divergence in behavior binds coronary sclerosis to the aging process in a manner more direct than pertains for hypertensive vascular disease.

The results of two other studies of the cause of untreated hypertension are deserving of consideration. That of O'Hare and Holden[5] at the Peter Bent Brigham Hospital is noteworthy in that it included 100 cases followed personally by the authors for periods ranging from 10 to 34 years. Of this group of 100 patients, 71 are still alive, and of these 71, only 5 are in "poor condition." Lest the optimism engendered by figures such as these should suggest that hypertensive disease adds to rather than subtracts from the number of years its victims survive, I would emphasize that in order for a patient to be included in this series, he had first to survive 10 years beyond the time his hypertension first came under the scrutiny of the physician-authors.

The effect of such a selection factor is placed in bold relief by the well-known study reported by Keith, Wagener, and Barker in 1939.[6]

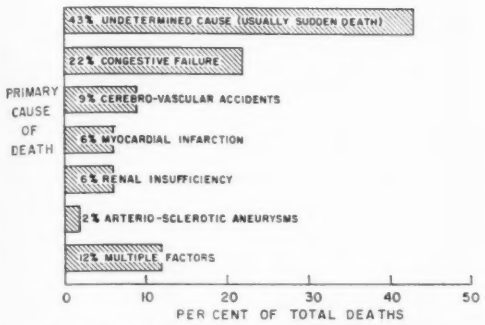
FIG. 2



Survival curves in the four groups.

Survival curves in the four groups of hypertensive patients as reported by Keith, Wagener, and Barker[6] in Am. J. M. Sc. 197:332, 1939, and reproduced here by permission of the publisher.

FIG. 3



Primary cause of death in a group of 500 patients. This figure was composed from data reported by Perera.[3]

The survival curves from the time when first the patients included in the series were examined are reproduced in figure 2. Note that all patients with hypertension of Group III and IV would have been eliminated from O'Hare and Holden's series since the longest period of survival for a patient in either group was slightly more than 7 years. Furthermore, by the end of 7 years, the survival curves for hypertensives of Groups I and II have flattened to a degree rendering them roughly parallel with the survival curves for nonhypertensive patients of like ages correspondingly charted.

There are certain deficiences in the study of Keith and associates, particularly as regards the arbitrarily selected date at which the individual patient entered the study, which date bore no fixed relation to the time he first had or even was first known to have had hypertension; and second, as regards the small number of patients included with Group I (10) and Group II (26) hypertension. However, as an attempt to give a faithful picture of the course of hypertensive disease, the study is free of the factors of selection operating in Perera's review where the patient had to die in order to be included, and the O'Hare and Holden study where he had to survive at least 10 years or be left out. Such are the distortions which beset the best and most intelligent efforts to describe the natural history of hypertensive disease.

II. *Causes of death in hypertensive vascular disease.*

In figure 3 is a bar graph derived from data reported by Perera[3] on a group of 500 patients having untreated hypertensive vascular disease followed until death occurred.

Perhaps the outstanding feature of these data is the 43% incidence of death from causes listed as "Undetermined," but which were "mostly instances of sudden death occurring at home or elsewhere." I would not have supposed that the frequency of abrupt demise in hypertensive vascular disease was as high as encountered in Perera's series. I did know that the incidence of sudden death in coronary disease was probably in excess of 25 per cent. Painter and associates[7] recently gave additional support to this impression when they reported that among 143 deaths from coronary disease in a carefully conducted community survey in North Dakota, 105 (73%) occurred before or within 24 hours of obtaining medical attention and 49 among these 105 (34%) were unattended deaths in patients who did not or could not obtain medical attention prior to death.[6]

Excepting from consideration this large group of cases labeled "Undetermined Cause," the distribution of the remaining cases in Perera's series among the predominantly cardiac, cerebrovascular, and renal causes is quite similar to the distribution found in comparable studies by other investigators.

In figure 4 is a bar graph composed from data presented by Smith, Odel, and Kernohan.[8] In this study, there were 100 cases each of hypertension Groups I, II, and IV, and 76 cases of hypertension Group III. The following points are noteworthy:

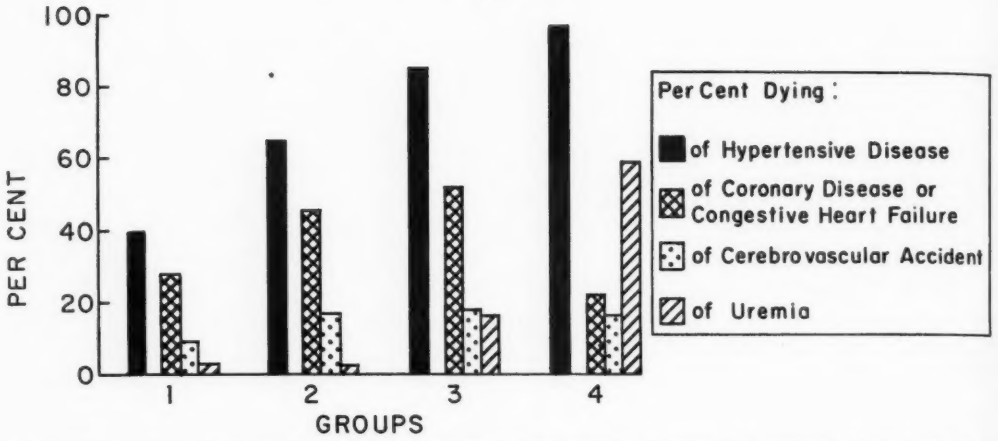
(1) As the severity of hypertension increased, the percentage of patients dying from causes directly related to hypertensive vascular disease also increased (from 40% in Group I, to 97% in Group IV).

(2) The percentage of cases dying from congestive heart failure and coronary disease increased from 28% in Group I to 52.4% in Group III, and then declined to 22% in Group IV.

(3) Death from cerebrovascular accidents occurred in 9% of cases with Group I hypertension; death from this cause rose to 17% among patients with Group II hypertension and remained at approximately the same percentage among patients with Group III and Group IV hypertension.

(4) Uremia was an infrequent cause of death among patients with hypertension Groups I and II (3 and 2% respectively), rose

FIG. 4



Causes of death among patients afflicted with hypertension analyzed according to severity of hypertensive disease under the classification of Keith, Wagener, and Barker. This figure was composed from data reported by Smith, Odel, and Kernohan.[8]

to 15.8% among Group III patients and to 59% among patients with Group IV hypertension.

These data provide statistical basis for the generalization that the causes of death among patients with benign hypertension reflect directly not the consequences of the underlying arteriolar disease, but rather, of the associated arterial disease, whereas malignant hypertension has consequences directly reflecting the effects of the arteriolar disease.[9]

The Relation Between Hypertension and Atherosclerosis

Certain items deserve now to be placed in apposition:

1. The incidence of benign hypertension is far greater than is that of malignant hypertension.

2. Death in benign hypertension is commonly an expression of the arterial lesions occurring in the afflicted individual.

3. If antihypertensive therapy is to prolong life among patients with benign hypertension, it will do so by retarding development of the arterial lesions.

4. Therefore, appraisal of evidence bearing on the relation between the level of blood pressure and the pathogenesis of arterial lesions is an appropriate element in any study of rationale for treating benign hypertension.

The lesions of atherosclerosis are distributed in a patchy fashion. That circumscribed changes in the arterial walls are an essential initial stage in the development of the atherosclerotic patch is likely. That mechanical stress is one of the elements contributing to this circumscribed primary change has been postulated. Hypertension would increase the degree of mechanical stress to which the arterial wall is subject and might be a critical element in determining the incidence and severity of the atherosclerotic lesion.

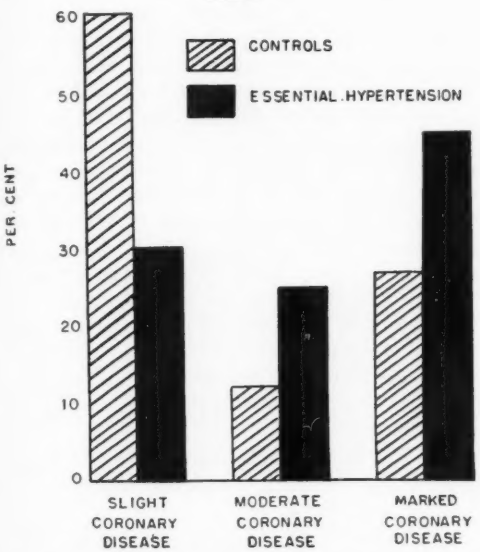
Review of contributions to evidence bearing on the possible accelerating influence of hypertension in the pathogenesis of atherosclerotic lesions has been made by Pickering,[10] by Waters,[11] and by Sokolow and Sanozaro.[12] Certain facets of this evidence will be considered here.

First, do degenerative arterial lesions occur in higher incidence in hypertensive than in normotensive patients or in experimental animals?

Davis and Klainer[13] have reported the results of a clinicopathologic study designed to answer this question insofar as it bears on the coronary arterial circulation. Figure 5, taken from their published account, indicates that whereas at necropsy slight coronary disease is about twice as common among 324 controls (230 men and 94 women) as among 137 hypertensive patients (90 men and 47 women), marked coronary disease is nearly twice as common among the hypertensive patients.

The coincidence of hypertension and coro-

FIG. 5

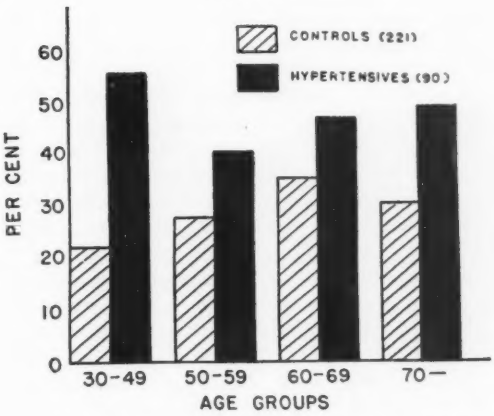


Severity of coronary disease as determined at necropsy among a control series of patients and a series having essential hypertension. (From Davis and Klainer,[13] Am. Heart J. 19:185, 1940, and reproduced here with permission of the publisher.)

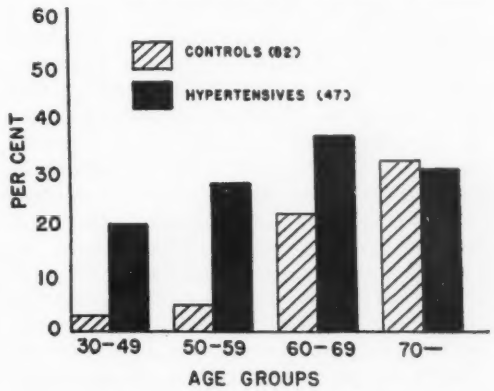
nary atherosclerosis is more strikingly reflected when patients with marked coronary disease are segregated from the control and hypertensive groups of patients for special analysis in relation to age of the patient. Figure 6, reproduced from Davis and Klainer's article, indicates that the coincidence of severe coronary disease and hypertension is particularly striking before the age of 50 in men and before the age of 60 in women. Noteworthy also is the fact that the incidence of coronary atherosclerosis in hypertensive women is significantly lower than in hypertensive men and about the same as in normotensive men. A sex related factor obviously continues to exert a significant influence on the development of atherosclerosis even among patients having hypertension. Davis and Klainer[14] did not believe their data supported the conclusion that hypertension causes coronary atherosclerosis. They noted particularly the absence of a correlation between the degree of hypertension and the severity of coronary sclerosis and the remarkably low incidence of coronary atherosclerosis among patients with severe hypertention of renal origin. They suggested that the frequent association of coronary atherosclerosis and hypertension represented the independent result of a common etiologic factor, and surmised that hypertension rather may be the consequence of renal or cerebral atherosclerosis than itself the accelerating factor in the atherosclerotic process. This surmise seems at odds with the authors' own data which indicate that men more commonly develop atherosclerosis than women whereas women more commonly become hypertensive.

Experimentally derived evidence on the relationship between hypertension and atherosclerosis has provided some interesting data, interpretation of which is still a subject for controversy. Outstanding among these reports is that of Wakerlin, Moss and Kiely[15] who observed that experimental renal hypertension

FIG. 6



Marked coronary disease in males.



Marked coronary disease in females.

Reproduced from Davis and Klainer,[13] Am. Heart J. 19:185, 1940, and reproduced here with the permission of the publisher.

accelerated the onset and accentuated the progress of experimental thiouracil-cholesterol atherosclerosis in dogs. They reported that the gross lesions are similar to those in human atherosclerosis in distribution and appearance, including with the severest lesions ulceration, calcification, and thrombus formation. Increased blood pressure appeared to be the essential potentiating factor in these thiouracil-cholesterol fed dogs, since the hypertensive state did not alter serum cholesterol levels, cholesterol phospholipid ratios, or low density lipoprotein concentrations.

But Wakerlin and his associates have made another and equally significant observation. Having provided support for the conclusion that hypertension markedly increases the severity of atherosclerotic lesions in the animal rendered susceptible to such lesions, they cite experience indicating that hypertension does not induce atherosclerosis unless the dog is rendered susceptible to such arterial disease by some such program as thiouracil-cholesterol treatment. Among 500 renal hypertensive dogs on whom necropsies were performed after 2 to 84 months in the hypertensive state, no atherosclerotic lesions were encountered. From this remarkable observation, the speculation might be derived that since hypertension, except for malignant or accelerated hypertension, commonly produces disability and death principally through its atheromatous complications, an effective means of preventing atherosclerosis would render high blood pressure an inherited variable of little more clinical significance than the inherited variability in tallness or shortness to which Pickering compares it.

Aggravation of atherosclerosis by hypertension is indicated also by the results of Deming and Daly.[16] They reported that rats placed on atherogenic regimens developed more atherosclerotic lesions at the base of the aorta and in the coronary arteries when hypertension was induced than when normotensive levels were maintained. These studies of the influence of hypertension on atherosclerosis in larger arteries are of primary importance in relation to the problem of vascular complications of so-called benign essential hypertension. Additional observations, more significant in relation to the pathogenesis of malignant hypertension, have been made on changes induced in the smaller arteries and in the arterioles by severe increases in arterial pressure. Byrom and Dobson[17] interpreted their studies on rats as indicating that an abrupt severe rise in arterial pressure can produce acute arteriolar necrosis of the arcuate interlobular and afferent glomerular arterioles. Masson and Corcoran[18] reported that in experiments of similar design, lesions restricted to the kidney consisted of hemorrhages, excessive distention of arteries and arterioles, edema of the intima resulting in partial obliteration of the lumen, and focal necrosis of the muscularis. These latter investigators studied also the influence of hydralazine induced control of hypertension on the vascular lesions in hypertensive rats. They found a strong correlation of reduction of blood pressure and decreased incidence and severity of vascular lesions.

These data bearing on the relation between hypertension and atherosclerosis may be summarized as follows:

(1) Atherosclerotic lesions occur more commonly among hypertensive than among normotensive representatives of the human race. Such lesions occur more commonly in the hypertensive than in the normotensive dog and rat experimentally rendered usually susceptible to atherosclerosis. Hypertension alone does not invoke atherosclerotic lesions in the dog.

(2) Both clinically and experimentally hypertension and atherosclerosis do not manifest a coincidence or common behavior suggesting their origin from one and the same cause. In the individual predisposed to atherosclerosis, hypertension accelerates development of lesions. Conversely, arterial and arteriolar lesions induced or aggravated by high blood pressure may induce an accelerated phase of hypertensive vascular disease.

(3) Certain human beings are strongly predisposed to the development of atherosclerosis and will develop major clinical consequences of the disease even though they remain normotensive. Certain other human beings, it appears, are strongly predisposed to elevations of blood pressure, and will exhibit major elevations over periods of many years with or without developing atherosclerotic vascular disease. Whereas atherosclerosis endangers life and health in the absence of hypertension, hypertension achieves its lethal effects by accelerating or inducing vascular changes. The nature of the vascular change is related to the degree

of elevation of the blood pressure. When mild or moderate hypertension exists for many years, the amount of atherosclerotic change is increased in the larger arteries, and coronary, cerebral and renal occlusive lesions endanger the life and health of the victim. When severe hypertension develops, arteriolar necrosis and destructive renal lesions commonly lead to death in uremia.

Untreated Hypertension Versus Treated Hypertension

Can our perceptions of the nature of untreated hypertensive vascular disease be sharpened appreciably by comparisons of untreated with treated series of hypertensive patients? Certain selected observations, I would conclude, merit presentation.

(1) Among patients with malignant hypertension, the period of survival can be prolonged by administration of those therapeutic measures generally deemed most effective in lowering the systemic blood pressure, namely, sympathectomy or present-day drug therapy.

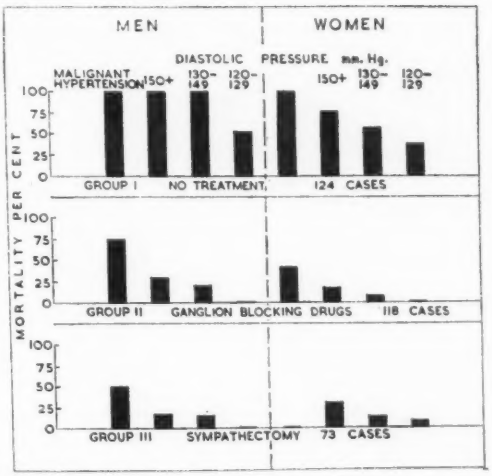
(2) Conversely, among patients with benign hypertension similar treatment has not been attended consistently by prolongation of life or protection against the several vascular lesions frequently complicating hypertension.

(3) Attention has been directed already to the point that the causes of death among patients with malignant hypertension reflect directly the consequences of the underlying arteriolar disease, whereas in benign hypertension they reflect the consequences of associated arterial disease. The indirection by which benign hypertension leads to death of its victim either obscures the contribution of antihypertensive therapy to survival or actually renders such therapy of negligible consequence to that survival.

In illustration of these points certain results from three excellent studies will be presented.

In figure 7, reproduced from Leishman's study[1] of a series of hypertensive patients accumulated in 1946 and subsequently, and observed medically until 1959 or until death of the patient, comparison is made of mortality percentages among three groups. Group I received no treatment, Group II received ganglion blocking drugs, and Group III were treated by sympathectomy. Treatment either by ganglion blocking drugs or sympathectomy was attended by a reduction of mortality rate

FIG. 7



Mortality rate in treated and untreated groups of hypertensive patients. (From Leishman,[1] in Brit. M. J. 1:1361, 1959, and reproduced here with permission of the author and the publisher.)

to one third or less than that occurring in the untreated cases in all categories except men afflicted with malignant hypertension. Note, however, that all patients included in this particular analysis had diastolic pressure of 120 mm. of mercury or more. They had comparatively severe hypertension.

Leishman's report affords support for optimism about the effect of good therapy on all forms of hypertensive vascular disease. Standing in contrast are the results reported by Perera.[19] Studies of carefully matched series of patients led him to conclude that while sympathectomy with or without a demonstrable reduction in arterial tension or antihypertensive drugs can modify the life span of some patients with the accelerated form of the disease, treatment does not appear to affect the average survival rate of patients with primary hypertension. This discouraging outcome on patients with primary hypertension pertained both with the uncomplicated and complicated forms treated by sympathectomy (Table 1). In a later report[20] of experience with drug therapy of primary hypertension in patients known to have had an elevated blood pressure for more than 5 years, and who had developed electrocardiographic signs of myocardial damage, Perera reported no significant improvement in survival rate of 29 treated as compared with 29 carefully matched, untreated patients. Not

TABLE 1

MATCHED CASES OF HYPERTENSION; EFFECT OF TREATMENT ON LIFE SPAN*

Diagnosis	*Treatment*	*No.*	*No. Dead in 10 Years*	*Av. Survival Fatal Cases (Months)*
1° Hyperten.	Symptomatic	40	16	48
	Sympathect.	40	14	51
			No. Dead in 5 Years	
1° Hyperten. Complicated	Symptomatic	20	12	37
	Drug	20	13	34
Accelerated Form	Symptomatic	25	25	11 (1-22)
	Sympathect.	25	16	13 (1-26)
Accelerated Form	Symptomatic	25	25	11 (1-22)
	Drug	25	17	10 (1-20)

*This table is from Perera,[20] in Tr. A. Am. Physicians 71:62, 1958, and is reproduced here with permission of the publisher and the author.

one of the 16 patients from the treated group nor one of the 16 from the untreated group died of renal insufficiency. In all cases death resulted from congestive heart failure, myocardial infarction, cerebrovascular accident, or ruptured abdominal aortic aneurysm.

From results such as these, one might be led to conclude that antihypertensive therapy can be justified certainly only among patients suffering from the malignant or accelerated form of the disease. But if no demonstrable prolongation of life and health attends present-day treatment of essential hypertension, the appropriate course for the future may be directed toward earlier and more complete treatment rather than toward the superficially reasonable course in the face of such frustration of no treatment at all. Two points may provide the needed substance to this argument.

First, even the skilled therapist must settle for a degree of antihypertensive therapy which is admittedly far from perfect. The criterion of a blood pressure of 160/104 mm.Hg. or less taken when the patient is standing, probably permits occurrence of considerably higher levels of pressure during periods of recumbency. These intermittent increases in pressure may be all that is required to foster progression of the atherosclerotic lesions which ultimately will result in the patient's death. A similar degree of control might be sufficient, on the other hand, to interrupt or reverse the course of accelerated hypertensive disease, centered as the lethal consequence of that process are at the arteriolar level.

Second, present-day therapy of hypertension may be inadequate to prevent acceleration of atherosclerotic disease because such treatment is begun too late. Mechanical stresses resulting from high levels of pressure may damage regions particularly subject to stretch when first those excessive tensions are developed, whereas to the rigid arteries of the patient in advanced hypertensive disease, reduction of pressure may be of little consequence.

Summary

In this review of untreated hypertension emphasis has been placed on the following features of this disease.

Primary or essential hypertension is a disease which begins almost exclusively during youth and early middle age.

After the hypertensive state is established, the victim survives an average period of 20 years, during the first two thirds of which time he is asymptomatic.

A course of benign and uncomplicated nature for 10 years implies a favorable prognosis, whereas progressive increase in pressure during a short period is likely to initiate a malignant or accelerated form of the disease which if not interrupted by effective treatment, will kill in haste.

Death in malignant or accelerated hypertension commonly is an expression of arteriolar damage leading to or attended by renal insufficiency progressing to the uremic state.

Death in essential hypertension results from atherosclerotic disease. Evidence, clinical, pathologic, and experimentally derived, indicates acceleration of atherosclerotic disease by hypertension. The two processes, hypertension and atherosclerosis, would appear each to ag-

gravate the other, but to arise from independent predispositions or sources.

Therapeutic measures which reduce blood pressure unquestionably influence favorably the prognosis in malignant or accelerated hypertension where arteriolar lesions are the common and direct cause of death; the influence of therapy on the survival of patients with benign hypertension is not established, death resulting commonly from the effects of atherosclerotic lesions related only in secondary fashion to the high blood pressure.

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Where Are the Early Carcinomas of the Prostate?*

JAMES F. O'MALLEY, M.D., and ROBERT H. OWENS, M.D.,
Kansas City, Mo.

The authors point to the dilatory efforts of the medical profession in the early diagnosis of the malignancy that stands second in the cause of death from cancer. They suggest means of stimulating interest among doctors in this curable disease.

THIS PAPER begins with a question common among urologists. The answer lies somewhere between general professional apathy and the incomplete physical examination. This apathy takes several forms—from the statement by an internist that "these old men have too many other problems," to the observation that their life expectancy is good even with the lesion. It is inconceivable and even inconsiderate to other physicians working to prolong man's useful life to disregard the second most prevalent cause of death from cancer in the male. A recent Public Health survey in Atlanta showed carcinoma of the prostate to have the highest incidence by primary site in the male, exceeding even cancer of the stomach.

The average urologist in private practice, in spite of diligent examination of his own and referred patients, seldom sees more than 3 to 4 operable prostatic cancers in a year. And this also is part of the enigma: we have a common malignant disease for which we know the cure, but for which we seldom have a chance even to try.

This situation, upon reflection, resembles the state of carcinoma of the cervix some 30 to 40 years ago. Unfortunately, no clubs have been organized among elderly men to have a yearly "cancer check" of their genital organs.

Tables 1 and 2 show the number of admissions for prostatic cancer at two large hospitals in Kansas City, Missouri, as well as their ages. They show the number of patients, their ages, and treatment. One is struck by the few curative procedures attempted in such a large group of patients. Those that are obviously too old, of course, did not just develop their disease and might have been salvaged at an earlier date.

TABLE 1

CASES OF PROSTATIC CANCER
1955 through 1959
(St. Mary's Hospital-104 Cases—St. Joseph's Hospital-135 Cases)

Operation	*Number*		*Comment*
	St. Mary's	*St. Joseph's*	
T.U.R.	52	80	
Suprapubic	5	9	
Retropubic (simple)	1	4	
Radical retropubic	3	4	
Radical perineal		1	
Orchiectomy	18	28	
Symptomatic	15	15	Stilphosterol x-ray transfusions
Terminal care	0	2	

Only 8 curative procedures attempted out of 239 cases of proven cancer.

Think of the public uproar if we failed to take advantage of modern medical treatment in other serious diseases. To what end are our lives to be prolonged only to fall prey to an increasing incidence of a malignant disease? It has been shown that this disease increases in incidence as age advances, and therefore it has been postulated that if a man lives long enough, he will develop cancer of the prostate.

In discussing the early diagnosis of this disease, the urologist traditionally describes

TABLE 2

AGE INCIDENCE OF 239 CASES

Below 50 years	3
50-60 years	8
60-70	74
70-80	109
80-90	42
90 and over	3

*Read before the Section on Urology, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

a single, small, solitary nodule as typical of the early process. Many, however, encouraged by their success, now believe that if the induration involves an entire single lobe of the prostate without any palpable extension, an attempted cure is feasible.

We may find prostatic calculi, the induration of infection, or a granuloma confusing at first, but the exact diagnosis can be determined by systematic examination. An x-ray film will reveal the calculi, and a biopsy of the suspicious area will reveal the offender in detail.

We prefer the transrectal biopsy technic, which has been worked out as follows: The patient's bowel is prepared by Neomycin and cleansing enemas the evening prior to biopsy. He is given a low spinal anesthesia and placed in the jackknife position. The rectal sphincter is dilated to four fingers and the prostate visually and palpably examined. A small incision in the rectal mucosa then allows biopsy of any portion of the prostate. A variation in technic is to use a biopsy needle directly through the mucosa without a preliminary incision. Either technic results in an adequate amount of tissue for confirmatory study.

When the lesion is confirmed by biopsy a decision must be made as to the future course, whether to attempt a cure or to initiate palliative therapy.

Most urologists use the following criterion in determining the feasibility of operation.

(a) The patient must be in good health with a life expectancy of over 5 years. We believe an arbitrary age limit of 65 is unreasonable when applied to a vigorous man of 70 who is physiologically much younger.

(b) There must be no evidence of spread of the cancer through more than one lobe of the prostate. This can also be evaluated by acid phosphatase levels and x-ray examination of the chest, spine, and pelvis.

Having established the diagnosis of operable carcinoma, the surgeon then decides upon the method to be used. The radical retropubic procedure popularized by Millin seems the most satisfactory to the urologist who does not frequently do perineal procedures. We plan to do the operation within 5 to 6 days after the transrectal biopsy. This has proven advantageous because there is a soft jelly clot at the biopsy site which has partially dissected the prostate from the rectal wall. A longer period would allow fibrosis to occur and make dissection difficult.

We use the Atherton sutures and do a cystostomy at the same time. The silk traction sutures make the anastomosis secure and seem to prevent stricture formation. The urethral catheter is left indwelling for 20 days. Our experience has been that this operation is tolerated well, and that the postoperative continence is surprisingly good. Two of our patients have volunteered the information that they have even attemptd a fairly satisfactory sexual experience.

Orchiectomy is not done routinely because, if the procedure is to be evaluated as an adequate one, no mutilating procedure is necessary. These patients are followed by yearly examination of the urine and x-ray studies.

The problem of the patient whose cancer is found following transurethral resection is resolved quickly and in the same fashion as the proven early lesion. We say *quickly*, because, technically, the inflammatory reaction around the entire prostate makes the radical procedure more difficult after transurethral resection. If the radical procedure is done within a short time, the reaction has not become fibrosed enough to be any factor.

As urologists we have made the members of the medical profession aware of the significance of hematuria. We should also make them more aware of the early cancer of the prostate.

A recent AMA meeting featured a booth where physicians could have their blood pressures taken. It was enlightening to find how few doctors follow their own advice about complete yearly check-ups. A perusal of the *AMA Journal* will reveal how many of our fellow physicians die of cancer of the prostate.

Since we are dealing with a serious disease of the male and since in so many the lesion has become advanced when first seen, we propose a novel way to impinge upon the doctors' consciousness. That to dramatize the early detection of prostatic cancer urologists set up examining booths at their various regional medical meetings. This could be done in a decorous manner and, if only one life were saved, would be worth the effort.

Summary

A number of cases of carcinoma of the prostate have been presented to re-emphasize to all physicians how few, unfortunately, have been diagnosed early enough to cure. The methods of diagnosis and treatment are discussed. A proposal that urologists set up diagnostic booths at local meetings is made. This would make more physicians aware again of the disease.

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The Clinical Usefulness of the Serum Leucine Aminopeptidase*

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The value of serum levels of this enzyme in diagnosis has been a matter of controversy. The studies of these authors again demonstrate its nonspecificity.

In 1958, Goldbarg and Rutenburg[1] first described a colorimetric method for the determination of the enzyme leucine aminopeptidase (commonly known as the LAP), and particularly stressed its usefulness in the diagnosis of cancer of the pancreas. They thought at that time that a negative test ruled out the possibility of pancreatic carcinoma. Since then, however, the serum levels of this substance have been found to be elevated in numerous other diseases of the hepatobiliary-pancreatic system and in normal pregnancy.[2-6] Its infallibility as a diagnostic tool in carcinoma of the pancreas has been disproven. We have studied this enzyme in a variety of patients with diseases of the liver, biliary tract, and pancreas over the last two years as well as in a number of control patients, and this is a summary of our experiences in the clinical application of this test.

Method and Material

Patients admitted to the Gastrointestinal Section, Veterans Administration Hospital, Richmond, were tested for serum leucine aminopeptidase activity by the method described by Goldbarg and Rutenburg, which consists of a relatively simple colorimetric procedure which will not be described in detail here.[7] According to more recent information, LAP is formed largely in the liver and excreted into the bile.[8] To a lesser extent it is formed also in the pancreas and kidneys and small intestine. It has been shown by histochemical staining that liver activity is located primarily in and about the bile-capillaries.[9] Kowlessar and associates[8] have shown electrophoretically that in normal patients, and in patients with disease of the biliary tract and pancreas, the major zone of LAP coincides with the post-albumin fraction of the serum. In those with either metastatic or parenchymal liver disease, there are two additional peaks of LAP suggesting that the abnormal peaks are derived from some change produced in the liver, either by stasis or by parenchymal disease. Over 350 determinations were done in normal controls and a variety of gastrointestinal diseases. There was no significant elevation in any except those involving the hepatobiliary-pancreatic system. Our range of normals followed those of Goldbarg and Rutenburg, with the upper limit of normal being 200 units for men. There were no women in this series.

Cirrhosis and Fatty Liver. The most interesting findings to us were those in patients with cirrhosis and fatty liver. Seventy-two patients were studied, some on repeated admissions, with the LAP and the standard liver function tests. The initial LAP on admission in these patients ranged from 132 to 888 GR* units with an average of 354, as noted in table 1. This same group of patients had an average alkaline phosphatase on admission of 6.5 Bodansky units, a bilirubin of 2.9 mg. per 100 ml., and a SGO transaminase of 52.4 units. The rise of the LAP in the serum in these patients closely paralleled the activity of the SGO transaminase, but at times was out of all proportion to the degree of jaundice or SGOT** activity (Fig. 1). The rate of the fall on the other hand, was much slower than that of the SGOT, and serum levels of LAP frequently remained elevated several weeks after the SGOT had returned to normal. This was the case in an alcoholic patient with cirrhosis who was admitted to this hospital on 6 oc-

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*Goldbarg-Rutenburg units.

**Serum Glulamicoxalacetic Transaminase.

TABLE 1

COMPARISON OF LEUCINE AMINOPEPTIDASE AND OTHER FUNCTION TESTS

		Tests—Average Admission Values			
Normals	*Number of Patients*	*LAP Under 200*	*Alkaline Phosphatase Under 4.5 (Bodansky)*	*Serum Bilirubin Under 1 mg. %*	*SGOT Under 40*
Liver carcinoma*	14	565	13.9	1.8	62
Viral hepatitis	11	330	8.8	7.0	226
Pancreatitis	10	266		0.6	
Cirrhosis—fatty liver	72	354	6.5	2.9	52
Cancer of pancreas—head,	8	665	16.3	7.2	55
—body and tail	3	315	8.3	0.6	

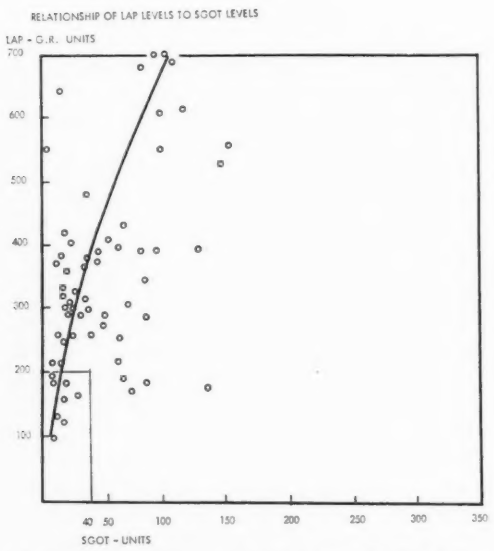
casions, each time having marked elevations of the LAP and only moderate elevations of the transaminase or bilirubin (Fig. 2). Three patients tested before and after portocaval anastomosis for bleeding varices showed no essential change in their LAP values.

Metastatic and Primary Carcinoma of the Liver. Fourteen cases of metastatic and primary carcinoma of the liver were studied, with the average serum LAP on admission being 565 GR units, the average alkaline phosphatase 13.9 Bodansky units, the average serum bilirubin 1.8 mg. per 100 ml., and the average SGOT 62 units. In this group of patients the LAP more closely paralleled the activity of the alkaline phosphatase than any other test. All but 3 of these patients had elevated LAP's on admission. In the 3 without an elevation, 2 had an alkaline phosphatase of 5.5 and 8 respectively, a mild elevation, and the third patient did not have one done. Of this same group of patients, 6 showed evidence of clinical jaundice on admission and 8 did not.

One patient progressed from a normal LAP of 156 to a high of 792 and death from metastatic liver carcinoma of the lung over a period of 5 weeks, and developed jaundice only terminally in the last several days. This test only roughly parallels serum bilirubin levels, and seems much more sensitive.

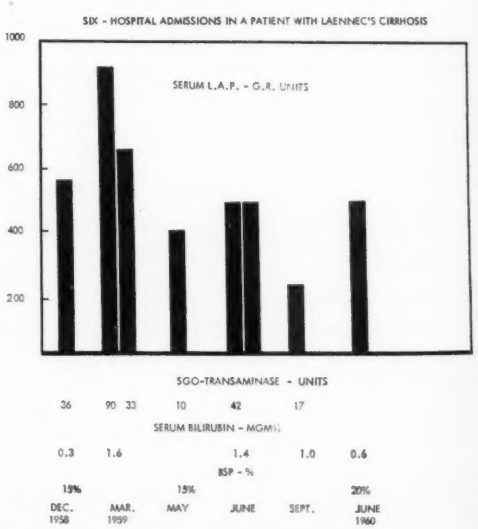
Other Biliary Obstructions. Other types of biliary obstruction were studied such as *"Thorazine hepatitis"* with admission LAPs of 463 and 636 in 2 patients, sarcoid granulomas of the liver with admission LAP of 552,

FIG. 1



Relationship between SGOT levels and LAP levels in patients with cirrhosis and fatty liver.

FIG. 2



Relationship of LAP elevations to other liver function tests on six admissions in a patient with Laennec's cirrhosis.

carcinoma of the common duct with a 984 LAP, and common duct stone with initial figures of 888 units in one patient and 1,272 units in another. This would tend to contradict, at least in these patients, the statement that benign disease of the biliary tract shows lower elevations than malignancy. It is a sensitive indicator of low grade obstruction of the common duct, such as is seen in silent stones and thus may be of real help in postcholecystectomy states without jaundice. When the LAP is elevated stones should be suspected.

Carcinoma of the Pancreas. Carcinoma of the pancreas was studied in 11 patients; in 8 of these it was in the head, and in 3 in the body and tail, admission figures were 144, 180 for those with carcinoma of the head was 665 GR units, for those with carcinoma of the body and tail, admission figures were 144, 180 and 264 respectively, the latter patient having metastases to the liver at the time of admission. In both of those with a normal LAP, the blood sugar was also normal, but the serum amylase was slightly elevated. In these 2 patients alkaline phosphatase was not done. All of the patients with carcinoma of the head of the pancreas had an elevated LAP and serum alkaline phosphatase. All but one of these also had an elevated serum bilirubin. It is hoped that the statement that "an LAP is all that is needed to rule out carcinoma of the pancreas," has been laid to rest by many other authors; however, we would like to reiterate this.

Viral Hepatitis. In 11 patients with serum and infectious hepatitis, the average LAP on admission was 330 units, with a range of 216 to 444. There was an average admission alkaline phosphatase of 8.8 Bodansky units, a total bilirubin of 7 mg. per 100 ml., and an average SGOT of 226 units. Other authors also found only moderate elevations in this disease.[3,5] The tendency of the LAP to fall more slowly to normal in hepatitis than the SGOT, was particularly notable in one patient with a chronic hepatitis whose SGOT fell slowly to normal but whose LAP remained over 400 for several months.

Pancreatitis. Ten patients with acute exacerbations of chronic relapsing pancreatitis were studied. The average admission LAP was 266 with a range of 108 to 396. Since all 10 of these patients were alcoholics, the average LAPs most probably reflected accompanying liver damage rather than pancreatitis itself. Several of these patients who had liver function tests done showed abnormalities. Interestingly, a group of 14 patients whose only diagnosis during hospitalization was chronic alcoholism, had an average LAP of 229 with a range of 162 to 300, also suggesting that this may be a sensitive indicator of liver injury.

Discussion

Since the early articles about the use of leucine aminopeptidases in liver and pancreatic diseases first appeared in 1957 and 1958, many have been written. Some have claimed that it is a foolproof method for the diagnosis of pancreatic carcinoma. At the other extreme it was suggested that elevations occurred in a sufficient number of diseases to make the test practically a sedimentation rate.[1,5,10] Our findings have confirmed probably what is the middle ground in this debate. We are in agreement with Shay, Kowlessar, and others that significant elevations of this enzyme occur only in the presence of liver involvement, either parenchymal or obstructive. We have not found, though admittedly our series is small, that the largest number of extremely high LAPs occur in carcinoma of the pancreas. Equally high LAPs have occurred in cirrhosis and fatty liver, and in metastatic liver disease. This is probably because most activity of the enzyme in this area is localized in the bile capillaries.

We have found that the test is most helpful under 2 circumstances. It is first of all useful in the patients who have elevated transaminases. Its rise parallels the rise of the transaminase and usually rises just as early. The fall, however, may lag far behind and thus give a more sensitive indication of continuing damage.

Second, we have found that in those situations in which the serum alkaline phosphatase is elevated, the LAP is elevated just as often, probably no more and no less. It has one advantage over the alkaline phosphatase in that it is apparently not affected by disease of the bone, although admittedly this is not frequently a problem. Helpful also is the technical simplicity of the test, requiring no unusual laboratory equipment.

Summary

The clinical usefulness of the LAP test in a variety of diseases of the liver, biliary tract, and pancreas has been studied in a number of patients. In liver disease it is of no help in differentiating parenchymal from obstructive

jaundice. It is helpful, however, in following the course and activity of the disease. It may be elevated in pancreatitis where its elevation is unrelated to the severity of the disease, but apparently is related more to alcoholism and possible liver damage. In carcinoma of the pancreas it is helpful only if obstruction of the biliary tract or liver metastases have occurred. In viral hepatitis its rise parallels that of the SGOT and its fall is frequently much slower, indicating a more sensitive index of activity. In a variety of other miscellaneous diseases of the liver with both obstructive and parenchymal damage elements, LAP levels are again of no differential value.

In short, the LAP test has been found to be much less specific than originally thought. It is a simple test to perform. Though it is not helpful in differential diagnosis, it is helpful in telling whether disease activity is present, improving, or worsening.

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Discussion (Abstract)

Dr. Martin Seler Kleckner, Jr., Paducah, Ky. I have found that the activity of leucine aminopeptidase does not specifically diagnose cancer of the head of the pancreas or extrahepatic biliary tract. The highest elevations of the serum leucine aminopeptidase have been found in patients with any type of obstructive jaundice, particularly common duct stone. The activity of serum leucine aminopeptidase represents another step in the investigation of several enzymes in the past several years to diagnose biochemically and more thoroughly diseases of the pancreas and the liver. To this date the diagnosis of irritable colon and carcinoma of all sections of the pancreas is inexact. A thorough history and physical examination and the conventional liver function tests take precedence over these serum enzyme activities. For the serum activity of LAP to be useful this test must be employed in a serial manner. It is in this way that serum glutamic oxaloacetic transaminase and serum cholinesterase have been very useful together with serum isocitric dehydrogenase in following the course of hepatic insufficiency. Our experience with elevated serum leucine aminopeptidase activity in the serial manner represents interference with biliary excretion of this enzyme resulting either from intrahepatic or extrahepatic obstruction in patients with primary or secondary hepatic disease.

Light Coagulation in the Treatment of Retinal Disease*

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The authors describe their experiences with a relatively new method of coagulation by light. It has its uses in retinal detachment, chorioretinitis and in the treatment of intraocular tumors in some circumstances.

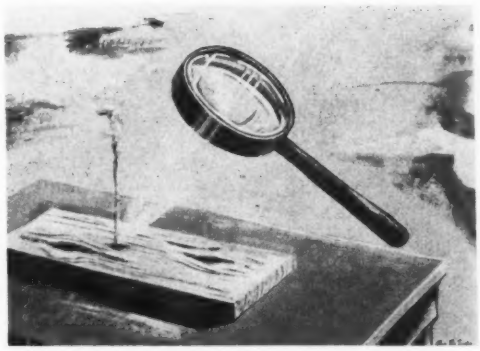
Development of the Instrument

LIGHT COAGULATION, or photocoagulation, as applied therapeutically in and about the eye, is a new technic developed since 1945 by Meyer-Schwickerath[1] of West Germany. In that year a solar eclipse produced macular damage in several human spectators who came to him for treatment. It then occurred to him that controlled artificial visible light of high intensity might be used to seal macular holes and cysts.

After much careful experimentation, involving solar mirrors and lenses, heliostats, mercury-vapor and carbon arc lamps, the principle of the "burning glass" (Fig. 1) was incorporated by Meyer-Schwickerath and the Zeiss Company into a reliable mirror ophthalmoscope whose irradiance can be increased for a fraction of a second to an intensity capable of coagulating the tissues focused in its tiny beam (Fig. 2). The light coagulator contains a high pressure xenon filled bulb, whose light intensity and beam size can be varied widely by a system of lenses, filters, and electrical circuits.

The spectrum of electromagnetic energy emitted at the end of the xenon light coagulator is between 350 and 1,000 millimicrons wave length, remarkably similar to the spectrum of a nuclear explosion flash or a black body at 5,800° K.[2-4] All other wave lengths are excluded since they would cause damage to the cornea by the ultraviolet rays and to the lens by the infrared rays. This "cold light," when absorbed by the pigmented choroid or iris, is transformed into heat energy at a maximum rate for this machine of 95 cal./cm.^{2}/sec. for a retinal image of 1 mm. size, according to Guerry and Wiesinger.[5]

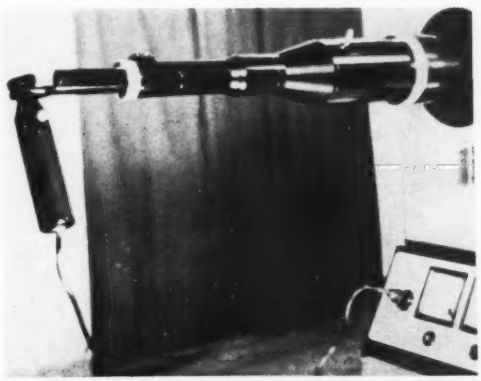
FIG. 1



"Burning glass"—principle of photocoagulation.

The nearly parallel rays of light are focused by the refracting media of the eye to a focal image of the light source on the retina. Detached retinas must be re-approximated to the

FIG. 2



Mirror ophthalmoscope of light coagulator (exposure button on handle).

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choroid before photocoagulation will produce a chorioretinal adhesion. At higher intensities the light produces actual cauterization necrosis, which is useful in destroying tumors.

The clear refracting media of the eye do not absorb a significant amount of energy at intensities and exposure times used normally.[1,4]

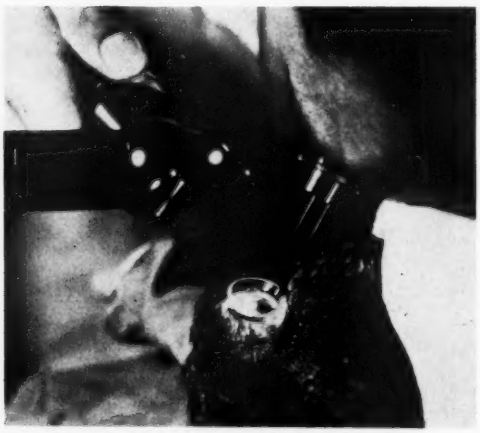
The mirror ophthalmoscope can be replaced by a convex lens and magnifying viewer for photocoagulation of the iris, conjunctiva, or skin.

Prerequisites for Light Coagulation

The refracting media of the eye must be clear. If the retina cannot be seen with a direct ophthalmoscope having a bright light, the success of light coagulation in the posterior segment is doubtful. Since the cornea must remain clear, all topical medication should be applied several hours before photocoagulation to allow time for the cornea to become clear again. Topical anesthetics are to be avoided, because their effects on corneal epithelium are particularly detrimental to its clarity. The drying effect of the light must be counteracted by dropping sterile balanced salt solution on the cornea every 5 seconds during photocoagulation. The anterior chamber and vitreous should be clear enough so little light will be scattered. A successful coagulation is sometimes possible despite these adversities, but care should be taken not to overheat the eye with high intensities or long exposure times.

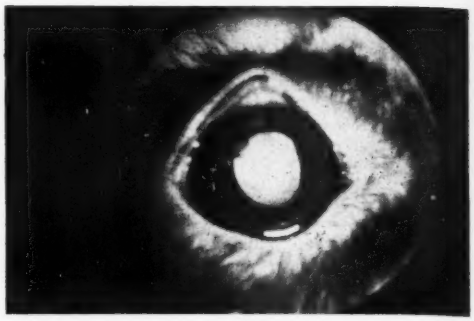
The lens must be clear to coagulate the retina. However, the periphery of the retina can be treated around a dense nuclear cataract.[6]

FIG. 3, A



Rabbit iris being coagulated with surface attachment.

FIG. 3, B



Optical iridotomy formed by photocoagulation in rabbit eye.

The iris must be maximally dilated, since the amount of light entering the posterior segment is linearly proportional to the area of the pupil. A long acting cycloplegic, such as atropine, may be supplemented by six applications of 10% phenylephrine HCl (Neo-Synephrine) to be completed at least 2 hours before treatment. Cycloplegia is particularly desirable in young patients to aid in accurate focusing of the light on the retina.

The retina must be closer than one diopter (0.3 mm. in an emmetropic eye) to the choroid in the area to be coagulated. Heat is conducted from the pigmented choroid to the translucent retina directly, so no adhesion would form between the two if the retina is detached. Peripheral holes and tears without detachment may be isolated with a ring of coagulation spots. If a small area of detachment around the hole or tear is present, the entire area may be surrounded by coagulation spots where the retina is still attached.

When coagulating the iris with the surface attachment, the cornea should be exceptionally clear and the anterior chamber deep enough so the cornea is not in focus at the same time with the iris, otherwise a corneal opacity may result. The plastic cooling chamber should be used and kept filled with balanced salt solution to keep the cornea moist and cool (Fig. 3, A). Coagulation of the iris should be limited to aphakic eyes (Fig. 3, B).

Akinesia of the eye is essential as a safeguard against the patient's suddenly looking at the light and obtaining macular damage. This is accomplished with a retrobulbar injection of

1% lidocaine. After small injections of 1% lidocaine in the lids and conjunctiva, retracting lid sutures and scleral sutures at the limbus are used to control the position of the globe.

General Instructions

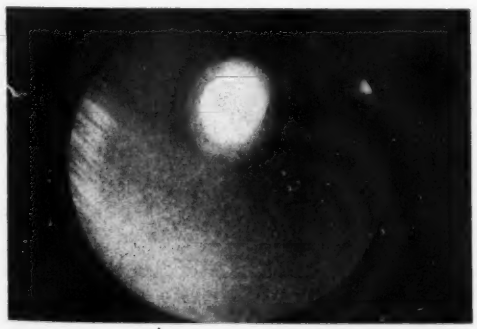
The instrument must be turned on with the controls set at "Basic II," and allowed to warm up for 5 minutes. This low setting allows proper ignition of the bulb and prevents an inadvertent over-coagulation on the first attempted exposure. The light becomes stable after 5 minutes.

After some experience one can accurately estimate the optimal exposure in each case. The beginner, however, should start by practicing with rabbits and should use the lowest possible intensities, gradually increasing the exposures so the white coagulation spot appears in 0.5 second (Fig. 4). Higher intensities are necessary with lightly pigmented eyes and in the periphery since the oblique angle of incidence required reduces the effective pupillary area. Scleral depression, for example, with a strabismus hook obviates some of this difficulty.[1,7]

Only in exceptional cases, for example with cloudy media or with tumors, is an "overload" setting necessary. Exposures of longer than one second with such high intensity creates the danger of damage to iris and lens through absorption by the iris. Inadequate dilatation of the pupil increases this danger.

When normal time and intensities suffice, a pause of about one second should be allowed between ensuing coagulations. With more intense coagulations longer pauses and vigorous bathing of the cornea are in order to cool the anterior segment of the eye.

FIG. 4



Blanched appearing coagulation of retina and choroid. (Blanching does not occur when choroid alone is coagulated.)

The size of the coagulation spots should be 3 degrees in most cases. This covers a spot 1 mm. in diameter on the retina of an emmetropic eye. A smaller beam tends to be scattered, and the heat at the choroid is carried away by the blood circulation. A larger beam tends to heat the iris and cornea unduly.

If the error of refraction of the area to be coagulated is more than 5 diopters, it may be corrected by contact lenses. Increments of less than 5 diopters need not be corrected.

Experimental Studies with Rabbits

Brown or chinchilla grey rabbits with darkly pigmented uveal tissue are particularly good subjects for study, since the absorption of the light from the light coagulator in their eyes is nearly identical with that of human eyes.[4] We gained proficiency in the use of the machine with many such rabbits before treating any human eyes. Generally less intensity is necessary in rabbits, since the pupil is larger and the focal distance is slightly shorter than in the human eye. The general considerations discussed herein are derived from these experiments as well as from clinical experience. Other investigators independently have confirmed these findings.

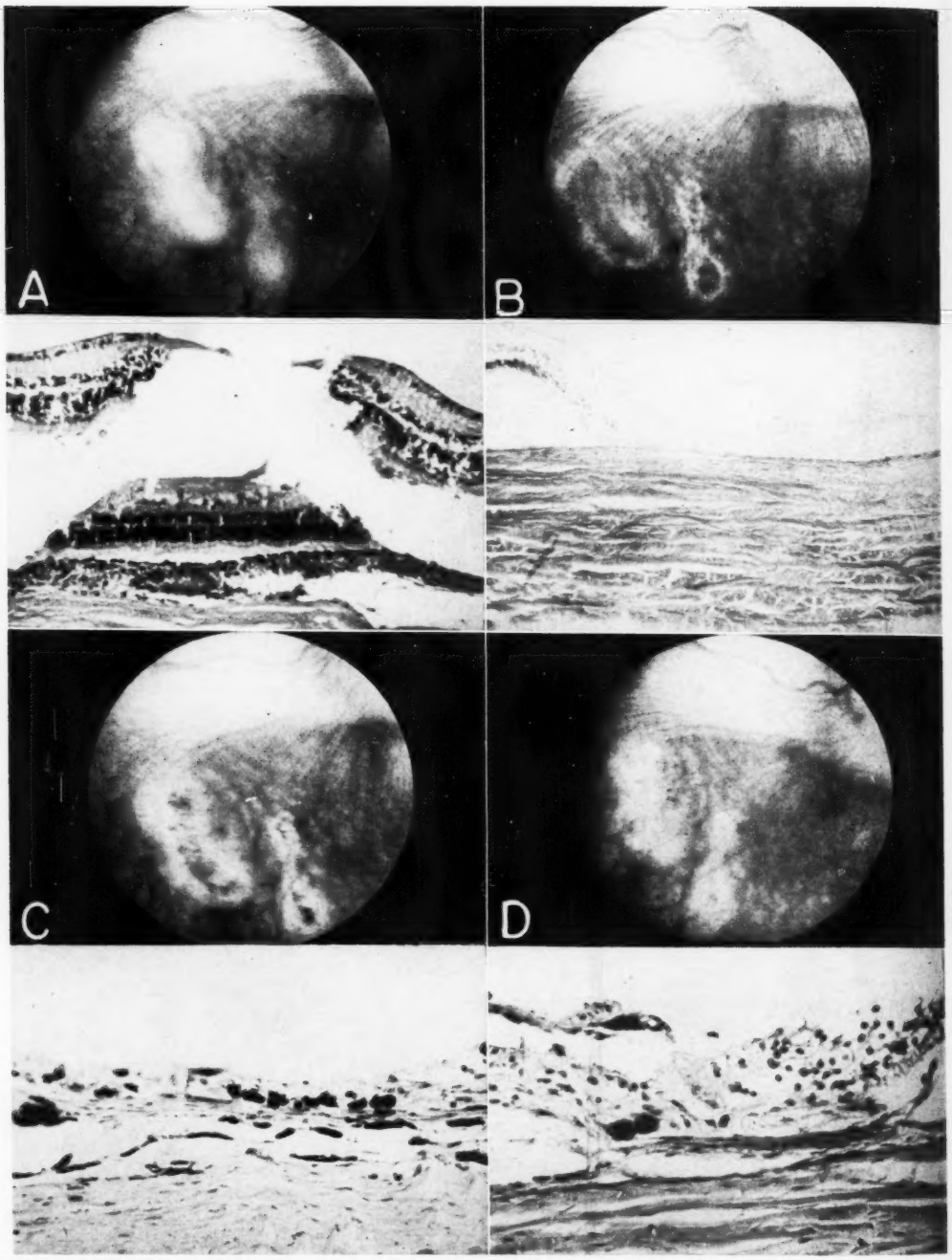
The course of retinal coagulation spots of varying intensity has been followed by fundus photographs and by histologic examination (Fig. 5). Immediately after light coagulation the retina appears white and elevated in a well circumscribed area. The retinal layers are seen to be edematous and somewhat thickened with a homogenous eosinophilic matrix. At this stage the retina is very friable and may easily tear at the edge of the lesion.

With optimal exposure the underlying choroid is likewise coagulated less severely than the retina, mainly in the choriocapillaris. The outer choroidal structures and sclera are affected only with very intense coagulations. This is in contrast to coagulation by diathermy whence the outer structures are more severely damaged.

After 2 to 3 days the retinal architecture becomes destroyed within the lesion and appears somewhat grey funduscopically. The retina is attached to the choroid only in the periphery of the lesion while the center is elevated by a small amount of subretinal fluid.

By 7 to 8 days the lesion appears flattened and sparsely peppered with pigment. Microscopically, the pigment is seen to be in the

FIG. 5



Fundus photographs and photomicrographs of "coagulation spots" in rabbit eyes. (Streaking is result of ocular movement.) (A) Immediately after photocoagulation spot appears blanched (above); retina is friable and edematous with antemortem detachment (below). (B) Three days after photocoagulation spot appears grey and elevated (above); retina is attached to choroid only at periphery of lesion (below). (C) Fourteen days after photocoagulation spot appears peppered with pigment (above); retina is firmly adherent to choroid by fibrous tissue (below). (D) Six months after photocoagulation some of pigment has absorbed (above); retina is somewhat cystic but firm fibrous scar is still evident (below).

retina which has become a layer of fibroblastic cells in a loose matrix sparsely attached to the choroid. After 10 to 14 days the scarring retina is seen to be evenly peppered with pigment. It is firmly attached to the choroid by fibrous tissue along the entire area of the coagulation spot.

After 6 months the spotty pigment has become absorbed except for a few clumps. A thin layer of dense fibrous tissue is seen to connect the retina and choroid along the area of the lesion. The thickness of the scar is about two thirds that of normal retina and choroid. Immediately peripheral to the spot the retina appears normal in all respects. Thus, it is evident that coagulated areas must touch each other to seal off a retinal tear or lesion.

Limitations, Contraindications, and Complications

Light coagulation is of no value in replacing an already detached retina. The danger of producing a retinal hole by focal necrosis and overheating of the iris and lens exists when an attempt is made to coagulate a detached retina by high intensity and long exposure times. If no blanching of the area being coagulated occurs within 0.5 to 1 second, a detached retina may be the cause; then one should proceed with great caution. Detached retinas must be reattached by bed rest or surgical procedures before light coagulation. One of the shortening procedures is preferred, such as scleral buckling, since light coagulation causes some shrinkage and slight folding of the retina, especially near the posterior pole of the eye.

A cloudy refracting medium *per se* is not a contraindication to light coagulation. However, so much light may be reflected and scattered that high intensities and long exposure times are required for an effective coagulation to occur, increasing the danger of atrophy of the iris and formation of lenticular and corneal opacities. However, this may be necessary in treating a malignant tumor which has not responded to other therapy, especially in an only remaining eye. Otherwise the risk is not justified.

If the pupil cannot be dilated maximally, a higher intensity is required for coagulation. The iris reacts to the extreme heat by constricting further and by subsequent atrophic changes. Contact with the lens by the overheated iris produces a small ring-shaped subcapsular opacity, the significance of which is not yet fully appreciated. This occurs after repeated coagulations with high intensities, usually in treating retinoblastomas. In those cases when no other therapy is possible, this heat damage is permissible so long as marked visual loss or secondary glaucoma is not induced.

Small intraretinal hemorrhages may occur often after light coagulation, but they absorb after one week without causing permanent damage. Large vitreous hemorrhages may occur immediately, or 2 to 6 days after coagulation of the wall of a large retinal vessel. Explosive disruption of the choroid, accompanied by a popping noise, may also produce a hemorrhage. The latter bleedings can be controlled by immediately coagulating the bleeding areas. Compression of the globe, as with an ophthalmodynamometer, may be necessary to halt blood flow and prevent the heat being carried away so cauterization of the bleeding point is possible. Such compression may be necessary to obliterate large vessels leading to intraocular tumors.

The most serious complication of light coagulation is the production of a generalized retinal detachment immediately after prophylactic treatment of threatening or beginning detachment. Areas of lattice or cystic degeneration should not be coagulated directly but should be surrounded with coagulation spots in normal retina. Since the adhesion formed between retina and choroid is a weak one at first, the shrinking of the retina may be sufficient to produce a tear in an area already weakened by degeneration or chorioretinitis.

Following treatment of tumors, particularly von Hippel's angioma, one may encounter a slight choroidal and retinal detachment caused by exudate which absorbs spontaneously after 1 to 2 weeks. This is called "ablatio fugax" by Meyer-Schwickerath.

Overheating of the anterior segment of the eye may produce a corneal opacity extending variously from the epithelium through the stroma to the endothelium. In addition, serofibrinous iritis, anterior and posterior synechiae, secondary glaucoma, atrophy of the iris, and progressive lenticular opacities may result.[7]

Hazards to the eye being treated may be categorized under too high an intensity or too long an exposure time to photocoagulation without

adequate pauses between exposures. Factors leading to overexposures are:

1. Light color of tissue to be coagulated.
2. Small aperature for light entering the eye.
   a. Constricted pupil
   b. Light off center of pupil
   c. Oblique angle of incidence
3. High myopia.
4. Extension of the focal distance.
5. Cloudiness of the refracting media.

The production of ozone by the light coagulator makes adequate ventilation of the room necessary to prevent respiratory difficulty in the persons present. The hazard of explosion with this oxidizer precludes the presence of all volatile combustible substances in the room. All anesthetics must be nonflammable. Fortunately, local anesthesia is sufficient except with children.

Should the patient look suddenly at the light during treatment, he may suffer a macular coagulation resulting in an absolute central scotoma. Prevention of this by akinesia and controlling sutures has already been mentioned. This has not occurred in our experience, and the opinion is expressed that it should always be prevented.

The light coagulator is not harmful to its operator or his assistants when it is used according to instructions. The operator is warned not to look at the xenon light. This is written in three languages on the side of the machine. Paraphrased it reads, "Do not look down the barrel even when the gun is not loaded."

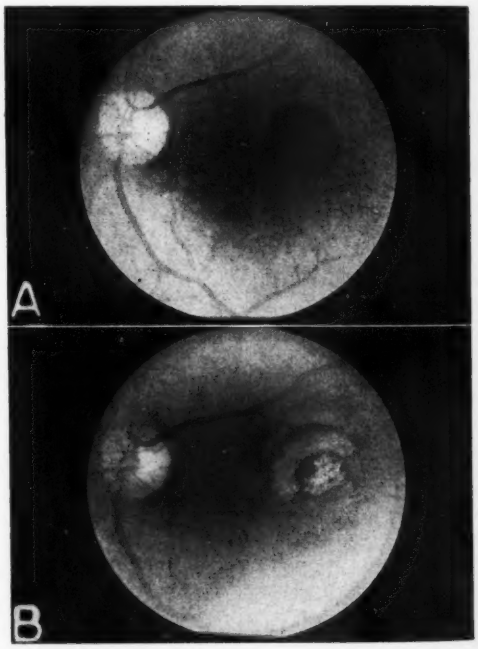
Specific Indications

Light coagulation was originally perfected to treat macular holes. Since such lesions seldom produce generalized detachment, they should be treated only when there is a detachment in the other eye or elsewhere in the same eye. However, one cannot predict the outcome in an individual case with a macular hole, and a detachment may be prevented by treatment. If the best corrected visual acuity is 20/200 or less, it is probably better to seal the hole, since visual acuity seldom gets worse than this and sometimes improves slightly after light coagulation. Macular holes should not be treated in eyes with visual acuity better than 20/200. The size of the coagulation should be slightly larger than the hole so as to coagulate within the hole and to blanch the rim of retina around it. Six such cases have been treated by us: 3 with detachment replaced by bed rest, and 3 without detachment. In one of the latter vision improved to 20/100 (Fig. 6).

In the cases in which retinal detachment is imminent, it can be prevented by photocoagulation while the retina is near the choroid and before the vitreous becomes turbid. However, often these patients are presented for treatment after the retinas have become detached. Prophylaxis by sealing off areas of retina affected by cystic or lattice degeneration, and peripheral holes or tears is effectively accomplished by photocoagulation with little risk as compared with surgery and diathermy. It is indicated in these conditions when there is a detachment elsewhere in the eye or in the other eye, prior to cataract extraction (especially in Marfan's syndrome and in atopic cataracts), or after perforating injury involving the retina.

Two cases have been described by one of us[8] in which a barrage of coagulation spots 360 degrees around the equator was placed in highly myopic eyes having peripheral retinal degeneration. No detachment has occurred in the 9 months since treatment.

FIG. 6



Macular hole (A) before, and (B) two months after light coagulation. (Vision improved to 20/100.)

Detached retinas may gradually become replaced with bed rest and binocular bandaging, whence photocoagulation is useful in sealing off holes or tears which had caused the detachment. Such conservative treatment depends on the position, extent, and duration of the detachment.

Light coagulation is useful in supplementing diathermy coagulation during or after operation. Tears not previously seen or inadequately surrounded may be sealed off in this way. Three such cases have been reported by one of us.[8] This technic is particularly valuable since one can be certain, under direct visual control, that the coagulation is placed posterior to the hole or tear.

Photocoagulation of the retina overlying an encircling tube may be preferable to diathermy in the base of the groove before burying the tube. Boniuk and Zimmerman[9] have reported 2 instances of enucleated eyes in which ischemic necrosis of the iris, ciliary body and retina followed encircling tube operations. Three rectus muscles were removed and diathermy was applied in the groove, including the areas of both long posterior ciliary arteries. Minimal photocoagulation does not affect the larger vessel layers of the choroid or the sclera, thus such embarrassment of blood circulation may be avoided. Such a procedure would have to be done during or soon after operation, since choroidal pigment tends to degenerate at the site of the tube.

We believe that postoperative care should be exactly similar to that after any form of operative treatment of retinal detachment. Bed rest and binocular bandages are in order. Corticosteroids and atropine should be used unless otherwise contraindicated.

Recurrent vitreous hemorrhages may be treated by light coagulation of the bleeding point after the vitreous has cleared.

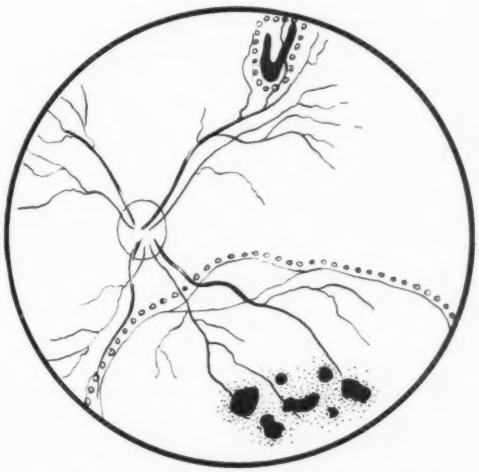
A 50 year old woman, who had three recurrent hemorrhages in 2 years with vision reduced to light projection, was found to have an inferior bullous retinal detachment and a superior temporal detachment with a tear at 12 o'clock. The superior detachment subsided on bed rest, after which the tear was sealed with a ring of photocoagulations, and the entire area inferior to the macula was isolated to the ora at 4 and 8 o'clock in a semicircle of coagulation spots. Several zones of neovascularization in this area were coagulated, since they were probable bleeding points. Postoperative care was bed rest and atropine eye ointment for 2 weeks. After 3 months the inferior detachment had flattened, no hemorrhage had occurred, and the vision was 20/50 (Fig. 7).

Intraocular tumors may be isolated from their environment by a ring of photocoagulations which obliterates their blood supply. Afterward the tumor may be cauterized by higher intensity coagulations. An exception to this procedure is von Hippel's angioma, which is treated first in the center, then in later sittings, further peripherally. Successful treatment of Eales's disease, Leber's miliary aneurysms, and hemangiomas of the retina and choroid have been reported.[10]

The treatment of malignant tumors is generally limited to those in the only remaining eye as a last resort before enucleation. Successful treatment has been reported with small retinoblastomas, malignant melanomas, and metastatic breast carcinomas.[10] We attempted the treatment of a retinoblastoma in the only eye of a 2 year old boy whose other eye had contained a retinoblastoma. The tumor had failed to respond to maximal roentgen ray and radiomimetic drug therapy. Its already large size and extreme peripheral position prevented surrounding it with photocoagulations and the eye was enucleated.

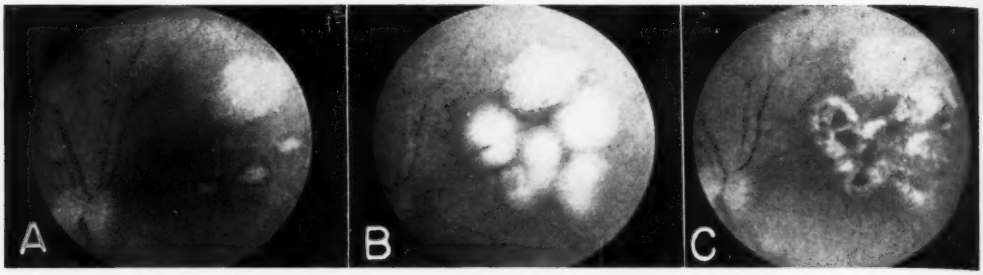
Lesions of focal chorioretinitis have been coagulated with varying results by Meyer-Schwickerath and Guerry. We have treated 3 such cases, all of which have showed no further activity, 2 after 9 months, the other after 3 months. In the first 2 cases the Sabin dye test

FIG. 7



Sketch of retina in case of detachment with recurrent vitreous hemorrhage. (Circles indicate photocoagulation.)

FIG. 8



Focal chorioretinitis (A) before, (B) immediately after, and (C) 9 months after photocoagulation.

and toxoplasmin skin tests were positive. No conclusion is yet possible (Fig. 8).

Treatment of the iris in our experience has been limited to optical iridotomy in updrawn iris in aphakic eyes. Five such cases have been treated, 2 successfully. One pupil appeared immediately with a loud popping noise; the other appeared 2 weeks afterward in the brown coagulated spot. The other cases had fibrous irides and shallow anterior chambers which prevented optical iridotomy. The successful treatment of xanthalasmas by surface photocoagulation has been described.[3,10]

Conclusion

An instrument designed to use high intensity visible light to fuse the retina and choroid in minute circumscribed scars is found to be a valuable adjunct to therapy of retinal detachment. Several other uses are becoming manifest in the treatment of intraocular tumors, chorioretinitis, certain skin lesions, and in performing optical iridotomy. The principle is that of the burning glass used to focus the sun's rays to ignite wood. The source of light in this apparatus is an electric arc enclosed in a quartz tube containing xenon gas under high pressure. This light is passed through an optical system of lenses and emerges via an ophthalmoscope mirror. The operator can direct a filtered portion of the beam into the patient's eye, and when it is accurately placed on the fundus he can switch on the full beam for a fraction of a second. The normal refractive power of the eye focuses the light on the retina, and a minute chorioretinal burn is produced. Several applications will seal off the area under treatment.

Credit should be given to Professor G. Meyer-Schwickerath for providing an instrument and technic which, when used properly and with caution, is definitely useful in selected cases.

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Cerebral Mucormycosis

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Attention is called to an unusual syndrome of fungal infection in the diabetic, especially one in acidosis. The fatal outcome upon its cerebral invasion is emphasized.

CEREBRAL MUCORMYCOSIS, a disease caused by a true fungus of the class Phycomycetes, is assuming an increasingly important role in clinical medicine.[1] Although Paltauf described the first case of cerebral mucormycosis in 1855 (Virchow's Archiv. für), more than three fourths of the 27 cases have been reported in the last decade. This probably represents a true increase in incidence and not merely an increase in awareness of the disease, since the organism is easily recognized on hematoxylin and eosin stained preparations.

The clinical characteristics of cerebral mucormycosis are frequently so typical that a clinical diagnosis can be reached and treatment begun before confirmatory evidence is provided by culture and biopsy. In this report, 3 case histories are presented and the literature reviewed.

Etiologic Agent

The causative agents of mucormycosis are true fungi of the class Phycomycetes, which is differentiated from the other broad class of true fungi in that the hyphae are lacking in septa. To this class belongs the order Mucorales and the family Mucoraceae. *Mucor* and *Rhizopus* are representative genera which are distinguished by their characteristic pattern of growth. Species identification is made by recognition of morphologic characteristics including sporulation, sexual and asexual.

Mucor and *Rhizopus* are ubiquitous in nature, occurring in the soil, in manure, on fruits, and are commonly recognized as "bread molds." Not infrequently they are contaminants in a bacteriologic laboratory, and have been commonly cultured from the nose and throat of normal individuals. These fungi are aerobic and grow rapidly on most bacteriologic media including Sabouraud's glucose agar, often filling the Petri dish by 5 days after inoculation. The genus *Rhizopus* is characterized by unbranched sporangiophores arising in fascicles from nodes along the stolons (runners). Opposite the sporangiophores are root-like projections called rhizoids. In contrast, in *Mucor* there are branched sporangiophores which arise directly from the mycelium which lacks rhizoids. The sporangiophores bear terminal globose sporangia, whose physical characters aid in species identification.

Pathology

Because the organism is ubiquitous in nature and is commonly found in the nose and throat of normal individuals, it is imperative for diagnosis that one demonstrate hyphae invading the involved tissue. The hyphae have a peculiar affinity for arterial walls with penetration of the intima resulting in thrombosis and infarction.[2] Later the lymphatics, veins and nerves may be involved. Characteristically there is very little host reaction to the fungus, although in the presence of infarction there may be an acute inflammatory response.

A common finding is intracervical thrombosis of the internal carotid artery or its major branches. Thrombosis of the nasal vessels accounts for the black, crusted appearance of the nasal septum and turbinates. In the brain there is often cerebral infarction, although direct invasion of the brain, with coagulation necrosis also occurs, most frequently in the frontal lobe. Pituitary involvement is not uncommon. The orbit may be soft and necrotic with destruction of the extraocular muscles and optic nerve.

The portal of entry in cerebral mucormycosis is usually the nasal cavity, with spread by blood vessels, lymphatics, or direct continuity to the paranasal sinuses, the hard palate, the orbit, and then to the brain and meninges.[3] The orbit may have been the portal of entry in some of the reported cases.

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TABLE 1

Source	Date	Age	Race	Sex	Concurrent Disease	Presenting Symptoms	Acidosis	Course	Treatment	Means of Diagnosis	Organs Involved
(1) Paltauf	1885	Adult	—	M	Intestinal ulceration	....	....	....	....	Necropsy	Brain, lungs, intestine
(2) Gregory, et al.[4]	1943	43	Neg.	F	Diabetes	Coma, loss of vision	+CO_2 6.0	Death in ? das.	Fluids, insulin	Necropsy	Nasal cavity, meninges, cavernous sinus thrombosis, internal carotid thrombosis, brain, pituitary
(3) Gregory, et al.[4]	1943	52	Neg.	F	Diabetes	Coma, swollen eye	+CO_2 6.5	Death 5 das.	Enucleation, fluids, insulin	Biopsy	Meninges, frontal lobe, orbit, ethmoid sinus
(4) Gregory, et al.[4]	1943	75	Cau.	M	Diabetes, cirrhosis	Confusion, swollen eye	?	Death in 2 das.	....	Necropsy	Orbit, optic nerve, meninges, cerebral vessels, pituitary
(5) Lecompte & Meissner[11]	1947	51	Cau.	M	Diabetes, cirrhosis, hemochromotosis	Coma, swollen eye, hemiplegia	+	Death 3 das.	Insulin, fluids	Necropsy	Meninges, brain, orbit
(6) Baker & Severance[12]	1948	3	Cau.	F	Diabetes	....	+?	Death ? das.	....	Necropsy	Thrombosis of internal carotid, orbit, brain, lungs, lymph nodes
(7) Wolf & Cowan[13]	1949	42	Neg.	M	Diabetes	Swollen eye, stiff neck	+?	Death 10 das.	Anticoagulants, antibiotics	Necropsy	Thrombosis of cerebral vessels & cavernous sinus, meninges, brain
(8) Stratemeir[14]	1950	32	Neg.	F	Diabetes	Swollen eye	+CO_2 4.5	Death 3 das.	....	Necropsy	Nasal cavity, ethmoid sinus, brain, meninges, thrombosis of cerebral vessels
(9) McCall & Strobos[6]	1953	18	Cau.	F	Diabetes	Coma, swollen eye	+CO_2 4.6	Living with residual neurologic findings	Insulin, fluids, anticoagulants, antibiotics, debridement, iodides, mycostatin	Culture & biopsy	Thrombosis of cerebral vessels, nasal cavity, sinuses, orbit, brain
(10) Martin[15]	1954	2½ mos.	Cau.	M	Diarrhea	Swollen eye	+CO_2 13.6	Death 4 das.	Fluids, antibiotics	Necropsy	Face, orbit, brain, meninges, thrombosis of internal carotid lungs, GI tract
(11) Kurrein[16]	1954	5 mos.	—	M	Acute nephritis	Swelling of eye	+	Death 3 das.	Fluids, antibiotics	Necropsy	Brain, meninges, thrombosis of meningeal vessels
(12) Bauer, et al.[2]	1955	25	Cau.	F	Diabetes	Coma, headache	+CO_2 5.2	Death 7 das.	Fluids, insulin, antibiotics	Necropsy	Meninges, brain, orbit
(13) Bauer, et al.[2]	1955	40	Neg.	M	Diabetes	Semicomatose	+CO_2 8.1	Death 6 das.	Fluids, antibiotics, insulin	Necropsy	Thrombosis internal carotid, meninges, orbit, brain, ethmoid sinus, pituitary
(14) Gunson & Bowden[17]	1955	8	Cau.	F	Chronic nephritis	Abdominal pain, vomiting	+?	Death 10 das.	Anticoagulants, antibiotics	Necropsy	Thrombosis of cavernous sinus & cerebral vessels, brain, meninges
(15) Harris[7]	1955	14	Neg.	F	Diabetes	Coma	+CO_2 11	Living with neurologic defect	Fluids, insulin, antibiotics, iodides, desensitization	Culture & biopsy	Cerebral vessels, nerves, orbit, palate, tongue, brain, sinuses

(16) Foushee & Beck[18]	1956	65	Cau.	F	? Diabetes, post cholecystomectomy, CA of kidney	RUQ pain	+ ?	Death 12 das.	Surgery, antibiotics, fluids	Necropsy	Brain, meninges, olfactory nerve, orbit
(17) Jackson & Karnauchow[19]	1957	20 das.	Cau.	F	Congenital heart disease, pneumonia	Cyanosis & dyspnea	?	Death 20 das.	Antibiotics, oxygen	Necropsy	Orbit, meninges, brain, cerebral vessels
(18) Merriam & Tedeschi[20]	1957	57	Cau.	M	Diabetes	Swollen eye, headache	+CO_2 4.2	Death 1 da.	Insulin, fluids, antibiotics	Necropsy	Thrombosis of cerebral vessels, brain, orbit, sinuses, pituitary
(19) Baker, et al.[1]	1957	Adult	—	—	Diabetes	....	....	Death ? das.	....	Necropsy	Sinuses, orbit
(20) Baker, et al.[1]	1957	62	—	M	Cirrhosis	....	....	Death ? das.	....	Necropsy	Thrombosis internal carotid, meninges, brain, orbit, sinuses
(21) Dwyer & Changus[21]	1958	46	Cau.	F	Diabetes	Unilateral ophthalmoplegia	+	Death 6 das.	Insulin, fluids, antibiotics	Necropsy	Thrombosis of internal carotid, nasal cavity, sinuses, orbit, meninges, brain
(22) Smith & Kirschner[3]	1958	72	Cau.	M	Diabetes	Swollen eye	+CO_2 17.8	Death 6 das.	Antibiotics, steroids	Necropsy	Thrombosis of internal carotid and ophthalmic vein, orbit, meninges, brain, pituitary
(23) Smith & Kirschner[3]	1958	57	Cau.	F	Diabetes	Coma	+CO_2 6.0	Death 42 das.	Fluids, insulin, antibiotics, mycostatin, amphotericin	Biopsy	Pulmonary artery thrombosis, nose, sinus, orbit
(24) Smith & Kirschner[3]	1958	6	Cau.	F	Diabetes	Swollen eye	+CO_2 5.2	Death 2 das.	Fluids, insulin, antibiotics	Necropsy	Internal carotid, cavernous sinuses and retinal artery thrombosis, orbit, brain, face and sinuses
(25) Borland[22]	1959	7 mos.	Neg.	M	Diarrhea, vomiting	Swollen eye	+CO_2 4.0	Death 6 das.	Fluids, antibiotics	Biopsy	Eye, orbit, brain, meninges, pituitary, sinuses, nasal cavity
(26) Long & Weiss[10]	1959	24	Neg.	F	Diabetes, pregnancy	Coma, shock	+CO_2 5.0	Death 3 das.	Fluids, insulin, antibiotics, cortisone, norepinephrine	Necropsy	Thrombosis of pulmonary and cerebral vessels, brain, orbit, mouth, nasal cavity, meninges, pituitary, lungs
(27) Smith & Yanagisawa[5]	1959	39	Neg.	M	Diabetes	Swollen eye, blindness	+	Death 4 das.	Insulin, antibiotics, KI	Culture & biopsy	Thrombosis of internal carotid, orbit, meninges, brain, sinuses
(28) Present	1959	59	Neg.	M	Diabetes	Blindness, swollen eye	+CO_2 18	Death 7 das.	Insulin, fluids, antibiotics, amphotericin	Culture & biopsy	Thrombosis of internal carotid, orbit, brain, meninges, sinuses, palate
(29) Present	1959	45	Neg.	M	Diabetes	Coma, swelling of eye	+	Death 4 das.	Insulin, fluids, iodides, amphotericin B	Necropsy & culture	Thrombosis of internal carotid, orbit, sinuses, meninges, brain
(30) Present	1959	65	Neg.	F	Diabetes, sickle cell trait	Coma, swelling of eye	+CO_2 3.0	Living with anatomic defect	Fluids, insulin, antibiotics, iodides, desensitization	Biopsy	Orbit, sinuses, nose, palate

Discussion

In each of the 3 cases of mucormycosis herein presented, the clinical findings were so suggestive that a tentative diagnosis was made before confirmatory evidence was obtained by culture and biopsy or necropsy. The cases fit the pattern described by Gregory and associates[4] in that all had uncontrolled diabetes, panophthalmitis, nasal involvement and sinusitis. Two of the patients had meningoencephalitis with thrombosis of major cerebral vessels. It was interesting that Cases 1 and 2 occurred only 37 days apart and that both were referred from the same southern Virginia hospital. In the patient who survived there was no evidence of meningoencephalitic involvement. All 3 patients were Negroes, two men and one woman, with ages of 45, 59 and 65 years. Physical findings were similar in each, with high fever, proptosis, ptosis, external and internal ophthalmoplegia, absent corneal reflex, and a purulent conjunctival discharge. As emphasized by Smith and Yanagisawa,[5] in each instance there was a black nasal mucosal eschar. All exhibited a brisk leukocytosis. There was cultural confirmation in 2 of the 3 cases.

In each of the 27 reported cases, there was some underlying, debilitating illness (Table 1). At least 22 of the patients were acidotic from diabetes, renal failure, or diarrhea. Intestinal ulceration, cirrhosis and congenital heart disease were associated disorders in other cases.

There is no predilection for age, sex, or race. Only two survivors of cerebral mucormycosis have been described,[6,7] death usually occurring within 10 days after the onset of symptoms. Only 6 of the 27 cases were diagnosed prior to death, and only 4 of these on clinical criteria. Orbital cellulitis, pansinusitis, meningoencephalitis and thrombosis of major cerebral vessels were present to some degree in almost all of the cases reported.

The *Mucor* and *Rhizopus* species are unique among fungi in several ways:

(1) They produce an acute, fulminating illness often simulating bacterial or viral infections.

(2) The organisms appear to attack the central nervous system of persons in acidosis usually from diabetes.

(3) There is a marked tendency to invade arteries with resultant infarction.

(4) In contrast to other pathogenic fungi they are aseptate.

(5) The hyphae are readily recognized in sections stained with hematoxylin and eosin.

To delineate the importance of certain predisposing factors, Baker and associates[8] conducted a series of illuminating experiments. Infection similar to that seen in humans was reproduced by intratrachael inoculation of *Rhizopus* into rabbits who were in diabetic acidosis as a result of acute alloxan poisoning. In rabbits who were chronically intoxicated and not acidotic, the disease could not be reproduced. Further, in cortisone treated mice the disease spread much more rapidly after intraperitoneal injections of *Rhizopus* than in control mice.[9]

Furthermore, the use of antibiotics has been said to render individuals more susceptible to fungal infections. However, each of the cases in this report presented with orbital swelling and other signs of mucormycosis before antibiotic therapy was instituted. This was also true of the majority of the previously reported cases. Since mucormycosis occurs in patients debilitated by pre-existent disease, its onset may well be overlooked. The rather constant findings of unilateral ophthalmitis, sinusitis, ulceration of the hard palate and a blackened nasal mucous membrane in the presence of a debilitating disease should suggest the diagnosis of cerebral mucormycosis and alert the physician to culture and biopsy of the lesion.

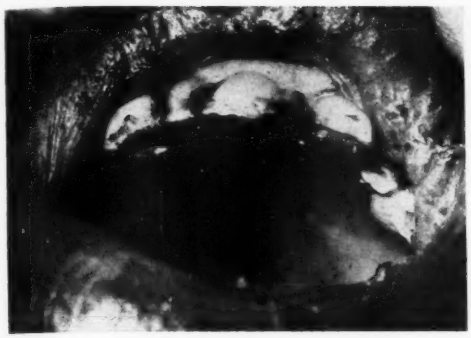
The nasal lesion may simulate idiopathic midline granuloma, rhinosporidosis, rhinoscleroma, thrombosed mucous polyps, syphilis, tuberculosis, or nasal tumors. Unilateral exophthalmos is also seen in suppurative sinusitis, mucocele of the sinus, cavernous sinus thrombosis, and retro-orbital arteriovenous fistulas, neoplasms and cellulitis.

In theory, treatment should be begun before there is evidence of meningoencephalitic involvement, although at the present time there is no treatment of proven efficacy.

The suggested therapeutic measures include treatment of the underlying disorder and correction of acidosis, omission of antibacterial agents and adrenocortical steroids, surgical excision where feasible and the employment of amphotericin B and possibly iodides.[10]

Case 1. D. W., a 59 year old Negro, was admitted to the Medical College of Virginia Hospital with a history of having had a bitemporal and retrobulbar headache for 2 weeks. Four days prior to admission, he

FIG. 1



(Case 1) Black eschar in the midline of the palate.

lost vision in the right eye and then suddenly lost sight in the left eye the following day. He had been a known diabetic for 3 years and had been receiving 0.5 Gm. tolbutamide per day.

Physical examination on admission revealed a well-developed, well-nourished negro man who was lethargic and confused. B.P. was 140/90, P. 100, and T. 101°F. There was bilateral proptosis, ptosis, and periorbital edema. The conjunctivas were chemotic and edematous with a purulent exudate. The corneas were dry, and the corneal reflexes were absent. The pupils were dilated, equal, and did not respond to light. There was absence of light perception. Funduscopic examination revealed white edematous retinas, grossly attentuated vessels, and a brownish-red color in the macular area bilaterally. There was a black eschar on the nasal mucous membrane, and there was purulent nasal discharge. A 0.5 by 3.0 cm. black ulceration was seen on the hard palate in the midline (Fig. 1). Nuchal rigidity was present.

On admission, the Hgb. was 12.0 Gm., WBC. count 22,400, urine showed sugar 3+ and acetone 1+; blood sugar was 300 mg. and BUN. 23 mg. per 100 ml., and CO_2 23 mEq./L. The spinal fluid had a ground glass appearance, was under normal pressure, contained 10,800 RBC. per cu. mm., 32 WBC. per cu. mm. of which 85% were neutrophils, 100 mg. per 100 ml. of protein, and was sterile. X-ray examination revealed clouding of the right maxillary antrum.

Course. Twelve hours after admission he developed a left hemiplegia, with left facial weakness, and the diabetes became very difficult to control. A clinical diagnosis of cerebral mucormycosis was made, and this was confirmed the next day by biopsy of the palatal ulcer. Microscopically there was evidence of acute inflammation with many lymphocytes, polymorphonuclear leukocytes, and plasma cells infiltrating the fibrous stroma. Gomori stains revealed broad, aseptate branching hyphae in the vessel walls and surrounding tissue. Culture of the palatal lesion grew *Rhizopus*.

Initial treatment consisted of fluids, insulin, streptomycin and penicillin. When a tissue diagnosis was made the antibiotics were discontinued, and treatment with amphotericin B and sodium iodide instituted. The patient's condition grew progressively worse, his coma deepened, and he died on the 7th hospital day. Permission for autopsy was not granted.

Case 2. T. Y., a 45 year old Negro, had been a known diabetic for several years, requiring 25 units of NPH. insulin twice daily. Eighteen days prior to admission to the Medical College of Virginia Hospital, a tooth was extracted, leaving him with severe left maxillary pain. Four days before admission to the hospital, he

FIG. 2

(Case 2) Note the left orbital edema and proptosis.

FIG. 3

(Case 2) View of the base of skull in the region of the sella turcica and sphenoidal ridges. The orbits and sphenoidal sinus have been unroofed. The pointer (lower left center) indicates the thrombosed left internal carotid artery. The necrotic contents of the left orbit are shown at the upper left.

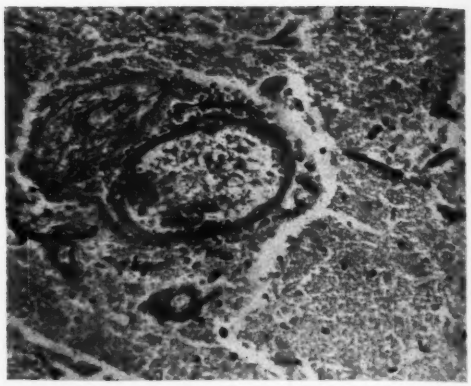
FIG. 4

(Case 2) View of basal surface of the brain showing the thrombosed left middle cerebral artery.

was admitted to a local community hospital with a history of swelling of the left eye, anorexia, lethargy and nausea and vomiting for 2 days. On admission there, his blood sugar was 255 mg. and CO_2 45 volumes per 100 ml., the urine containing 4+ sugar and 4+ acetone. He was treated with fluids, insulin, penicillin and tetracycline. Because he was becoming progressively less responsive, despite the fact that he was no longer ketotic, he was sent to the Medical College of Virginia Hospital.

On *physical examination* at the Medical College of Virginia Hospital, the patient was a deeply stuporous, slender, well-developed negro man with a B.P. of 110/70, P. of 84, R. of 24, and a T. of 102.4°. The skin was warm and moist. There was ptosis and proptosis of the left eye with blood oozing from the inner canthus. Conjunctival hyperemia and edema was noted in that eye (Fig. 2). The left pupil was dilated, but neither pupil reacted to light. Bilateral cataracts were present. The fundi were not seen. Crusted black material was noted in both nostrils, and a 3 by 3 cm. crusted ulcerated lesion was observed on the hard palate. The left maxillary gingiva was swollen, indurated and red. Nuchal rigidity was present. The carotid pulsations were equal. There were bilateral moist rales, and a harsh grade II early systolic murmur was heard at the second left interspace to the left of the sternum. Examination of the abdomen was not remarkable. Neurologic examination revealed a right-sided flaccid paralysis. The deep tendon reflexes were hypoactive throughout and absent in the right lower extremity. A Babinski reflex was present on the right.

FIG. 5



(Case 2) Photomicrograph of a thrombosed cerebral vessel. Broad, aseptate hyphae can be seen in the lumen and wall of the vessel as well as in the substance of the brain.

At the time of transfer, the Hgb. was 12.6 Gm., WBC. count 12,500 per cu. mm. with 80% neutrophils; the BUN. was 9 mg. and blood sugar 233 mg. per 100 ml.; CO_2 was 34 mEq./L. The urine showed sugar 4+ without acetone. The cerebrospinal fluid contained 23 RBC. per cu. mm., 256 WBC. per cu. mm. with 82% polymorphonuclear leukocytes, and 20 mg. of protein per 100 ml.

A diagnosis of mucormycosis was made on admis-

FIG. 6

(Case 3) The sinus cavity can be seen through the defect at the inner aspect of the right eye.

sion. Although multiple biopsies and cultures were nonrevealing, the patient was treated with amphotericin B and sodium iodide. His condition deteriorated rapidly, and he died on the 4th hospital day.

Necropsy Report. Except for some hemorrhagic cystitis and mucopurulent exudate in the bronchi, the gross abnormalities were limited to the cranial contents. On opening the calvarium the brain was seen to be markedly edematous and extremely softened, particularly in the region of the left frontal lobe. There was a serous exudate over the base of the brain and marked congestion of all basal blood vessels. The inferior surface of the left frontal lobe was liquified. There was marked congestion and increase in pressure in the left orbit, and the tissues of the orbit were friable and necrotic (Fig. 3). A gelatinous material was noted in the sphenoidal sinus. A grayish-red thrombus was seen in the left internal carotid artery, extending into the anterior and posterior communicating arteries and into the middle cerebral artery (Fig. 4). Upon sectioning the brain, the softening was noted not only to involve the frontal lobe but also the regions of the thalamus, hypothalamus, striate nucleus, caudate nucleus, and mid-brain structures.

Microscopic Examination. The lungs showed diffuse congestion and acute bronchopneumonia and bronchitis without evidence of specific infectious agent. The pancreas showed diffuse atrophy and fibrosis with the islets of Langerhans staining poorly. The main findings were again in the cerebral contents. Ischemic necrosis of the retro-orbital muscle and adipose tissue was evident. There was an infiltration, primarily by neutrophils but with large numbers of mononuclear cells and lymphocytes. Numerous broad, aseptate hyphae, 10 to 14 microns in width, were noted in that region. These fungi were noted particularly in the region of arterial walls and often invaded the lumen and produced thrombosis. Hyphae were also noted in the perineural lymphatics, in the optic nerve, central retinal artery, and in the scleral tissues. Examination of the thrombosed cerebral arteries and internal carotid artery showed hyphae in the wall and lumen (Fig. 5). There was also thrombosis of the cavernous sinus. The brain itself showed widespread ischemic necrosis of the left frontal, parietal and temporal lobes, with many hyphae noted in these areas. A 1 cm. low grade astrocytoma of the cerebellum was noted in the region near the dentate nucleus.

Cultures were taken postmortem for routine organisms and for fungi, but neither *Mucor* nor *Rhizopus* was isolated.

Case 3. S. T., a 65 year old negress, apparently had been in good health with no known diseases until several days before admission to a local hospital because of confusion, high fever, and anorexia. On admission she was dehydrated and comatose, with moderate swelling of the right eye and a purulent conjunctivitis. The right pupil reacted poorly to light. Laboratory examination revealed a Hgb. of 8.0 Gm., WBC. count of 41,000, blood sugar 340 mg., N.P.N. 55 mg. and CO_2 6 vol. per 100 ml. Urinalysis contained sugar 4+ with acetone 4+. The cerebrospinal fluid was normal. Culture from the eye lesion grew *Esch. coli* and paracolon bacillus. There was x-ray evidence of osteomyelitis of the nasal bones and of right maxillary sinusitis. Treatment consisted of fluids, insulin, and multiple antibiotics. The patient's diabetes was quickly controlled, and her general condition improved remarkably, except that the osteomyelitis grew progressively worse.

She was referred to the Medical College of Virginia Hospital for further treatment after 7 weeks in the local hospital. On admission, the B.P. was 120/70, P. 20, R. 18, and T. 102°. There was right-sided proptosis, ptosis, external and internal ophthalmoplegia, conjunctival injection, and a 1 by 1 cm. fistulous tract in the region of the inner canthus, communicating with the nasal cavity and draining thick, greenish exudate. A dark black eschar was noted on the nasal septum. Also an antropalatal fistula draining purulent material was observed. Laboratory findings on admission revealed a CO_2 of 28 mEq./L., a WBC. count of 11,000, Hgb. of 8.2 Gm., and a positive sickle cell test. Hemoglobin electrophoresis revealed hemoglobin S and A. There was x-ray evidence of pansinusitis.

Initial treatment consisted of chloramphenicol, tetracycline, and ferrous sulfate. Although a clinical diagnosis of mucormycosis was suggested on admission, cultures were consistently negative. On the 15th hospital day, it was noted that the greater part of nasal septum, the anterior wall of the sphenoidal sinus, and the entire right maxillary sinus were necrotic. On the 40th day large sequestra were removed from these areas, and the lesions thoroughly debrided. Microscopic sections from these sequestra revealed broad aseptate hyphae having affinity for blood vessel walls.

The patient was discharged on the 42nd hospital day. She had been followed in the Outpatient Clinic for 2½ years with good control of her diabetes and no evidence of residual infection (Fig. 6).

Summary

1. Cerebral mucormycosis is caused by true fungi of the genera *Rhizopus* or *Mucor*. There appears to be a true increase in incidence.

2. Three cases of mucormycosis are reported. The two with cerebral involvement died, while the other with antral, nasal and orbital infection survived. In each case the diagnosis made clinically was confirmed by histologic study.

3. The literature is reviewed and emphasis placed upon the typical clinical picture of a previously ill patient, usually acidotic, most often from diabetic ketosis, who develops proptosis, ophthalmoplegia, sinusitis and a black nasal eschar.

4. Only 2 of the 29 cases of cerebral mucormycosis have survived. Early diagnosis on a clinical basis would allow more prompt institution of therapy, although the efficacy of the suggested regimen is unproven.

Acknowledgment: Grateful appreciation is expressed for the aid of the Department of Pathology of the Medical College of Virginia and the aid of Dr. Miles Hench, Chief Hospital Microbiologist.

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HOTEL RESERVATION APPLICATION FORM

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APPEARS IN THIS ISSUE

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Recognition and Management of Depressive Reaction*

CHARLES B. FULGHUM, M.D., *Atlanta, Ga.*

The belief is expressed that the depressive reaction is too frequently missed by the attending physician. The psychodynamics are described for an understanding of the condition leading to proper management.

INTEREST IN THE DEPRESSIVE REACTION has reached an all-time high in recent months. In every psychiatric journal and many nonpsychiatric journals, there are reports of the efficacy of antidepressant drugs and the high incidence of depression in all areas of medical practice. This interest is apparently being stimulated by the drug industry, impatient with general physicians whom they claim do not appreciate the prevalence of the depressive reaction and thereby fail to prescribe their new "psychic energizers."

To review the incidence figures: Culpan and Davies[1] found 51% of newly referred medical outpatients had psychiatric illness, most of whom they state manifested depressive symptoms. Zwerling[2] found 15.5% of patients in the surgical clinic to have neurotic and psychotic depressions. From our own incomplete studies we estimate that about one third of medical admissions to a general hospital have a depressive reaction.

The purpose of this paper is:

1. To give a description of the depressive syndrome so general physicians can be more accurate in their diagnosis.

2. Make the psychodynamics of depression more precise.

3. Make some suggestions about treatment based on an understanding of psychodynamics so it can be more rational.

The most striking aspect of the depressed patient is usually his emotional state. It may be one of overt depression or sadness, but it is as often anger, irritability, guilt and, at times, anxiety. Accompanying these emotional symptoms or prior to their development, there may be many physical symptoms such as fatigue, loss of appetite, weight loss and sleeplessness. Frequently such physical symptoms as aching muscles, gaseous distention, constipation, epigastric distress, frequency, impotence, frigidity, menstrual disturbances, hot flashes and headaches are symptoms of a depressive reaction.

The foregoing clinical picture is well known to every physician. He is aware that these symptoms are most often manifestations of psychiatric disturbance. In our experience, however, the general physicians are prone either to vaguely diagnose with the term "psychosomatic" or treat the symptoms nonspecifically without a diagnosis. These symptoms yield temporarily to vitamins, "liver shots," thyroid and "psychic energizers," but permanently to none of them.

If one is willing to accept symptom control as adequate treatment, the depressed patient can be and is being treated. But the depressive reaction can be precisely diagnosed, specifically treated and cured.

Treatment of any disease, if it is to be rational, must be based on an understanding of the basic mechanisms of the disease. The basic mechanism of a depression is that the patient feels he is in an emergency situation. The emergency situation can either be real or imagined. For example, the man who loses his wife may become depressed. This is a real emergency. The student who fails an examination may feel that he will lose the love and respect of many of his friends. This seems more of an imaginary danger. The patient reacts to his emergency situation, be it real or imaginary, with a depressive reaction which is essentially an appeal for help. In the initial stages of depression, while in the emergency situation, the patient turns to someone on whom he is de-

*Read before the Section on Neurology and Psychiatry, Southern Medical Association, Fifty-Fourth Annual Meeting, St. Louis, Mo., Oct. 31-Nov. 3, 1960.

pendent to help him out of the emergency situation. Frequently a husband will turn to a wife, or a wife to a husband. A student will turn to his family. If help is not forthcoming, the patient turns to other people to help him in his emergency situation. We are concerned with people who turn as patients to their doctors.

Though these patients are primarily depressed, they usually present themselves with more socially acceptable symptoms asking for help. If help is not forthcoming, the patient becomes angry at the person who is not helping him. It is clear that if the patient is in an imaginary dangerous situation, no help is possible since one cannot help people out of imaginary dangers, and if the patient is in a realistically dangerous situation, he must get himself out of it. It is, therefore, rare for anyone to whom they turn for help to give them the help they seek. The patient, at this point, becomes angry with disappointment.

Long experience has taught him, however, that if he is angry at the person from whom he seeks help, he will be rejected and any possibility of help is lost forever. He, therefore, hides his anger, and if the anger is very intense, agitation is superimposed on the depression, manifesting itself as restlessness or anxiety in a more demanding patient. As the anger and frustration mount, a new symptom appears—guilt. It is clinically apparent and the patient is uncomfortably aware of it, but not its cause. The patient's guilt is related to his unconscious anger at his dependent object. The patient knowing that he should not get angry with another person, especially a person on whom he depends, is only aware that he feels guilty and searches his past for some explanation of his guilt. It is for this reason that patients are preoccupied with past failures and moral transgressions.

The rational treatment of this illness is based on these psychodynamics. The patient, however, is not asking for rational treatment; he is asking for magic. The patient assigns physical symptoms to his general feeling of discomfort and is in a sense asking that the physician, without looking past the primary symptoms, adequately treat not only the vague general discomfort but remove the source of that discomfort, the real or imagined emergency situation.

The physician who is unaware of the magic for which the patient asks, hears only the patient's words, a rather long recital of challenging complaints. Initially he is patient, interested, challenged, and solicitous, but gradually he very humanly becomes bored and irritated by this "crock" and refers him to a specialist.

With an understanding of the patient's dilemma, he need not be referred. The vast majority of depressive reactions are treated by nonpsychiatric physicians. They can, as well, be treated with a specific diagnosis and a specific treatment.

In the beginning when the patient appeals for magical help, the physician in a clear, firm way must point out that such magic help is not available. This means an explanation that there is no vitamin, no shock, no drug, and no word that can be said that in a magical way will cause the disappearance of the patient's symptoms. The patient at this point will become angry at the physician and will in some way express dissatisfaction. This must be accepted and dealt with by the physician with the understanding that the anger results from frustration and disappointment, and that there is no magical solution to the problem. It may take several interviews or visits by the patient and repeated pointing out that there is no magical solution. The next step in therapy is to examine with the patient what the emergency situation is. For example, the woman who loses her husband becomes profoundly depressed and after her husband has been dead for three months is still depressed. She feels that in this emergency situation she cannot survive without her husband; her life has come to an end. It is well known that thousands of widows do manage to survive and they do manage to make a new life for themselves. After one has dealt with the magical expectations that the physician can solve her problems and bring her husband to life and magically cure her depression, and once this is discussed with the patient openly on several occasions, the patient will begin to become dependent on the therapist. This should be permitted. During the time, however, that the patient is being supported, she must be encouraged to seek a new life for herself. It should be pointed out over and over that life for her has not come to an end. Stepwise, the treatment is:

1. Allow the patient to be dependent on the therapist.

2. Point out that there is no magical cure for the problems.

3. Look at the emergency situation, and point out to the patient that an insoluble emergency does not exist. Either the emergency does not exist or the patient has the resources to adapt to the world on his own without help from anyone else.

The following case illustrates this approach to a depressed patient.

The patient was a 50 year old woman whose husband had recently died. She was profoundly depressed and had been completely incapacitated since her husband's death. Prior to his death there had been great hostility and conflict between them, and at the time of his death she felt quite guilty for all her imaginary past transgressions. She felt and stated that she was helpless, her life had come to an end, and she had no resources. She could not work or keep house; all she was doing was staying in bed. She was admitted to the psychiatric floor in the hospital and soon developed a dependent relationship with her doctor. In the early part of her therapy, she appealed again and again in a helpless way for magical help. It was repeatedly pointed out that there was no such thing as magical help, no shocks or words or medicine that was going to make her well. She was first told, then shown, that she was able to make a new life for herself. After a period of 3 or 4 weeks, the patient became quite dependent on her physician and began to recover from her depression. She began to accept the reality of her situation and talked of looking for a job. At the end of a month, she went home, continued to see her physician who continued encouraging her. At the end of 3 months, her self-esteem was much higher, she had begun to find new interests in life and her neurotic depression was gone.

This treatment was based on a rational understanding of the psychodynamics. Again:

1. The patient was dependent and the physician allowed her to be dependent.

2. The patient appealed for magical help and was told many times that no such magical help was available.

3. The patient was encouraged to use her resources to make a new life for herself and to face what she regarded as a dangerous situation.

Summary

The incidence of the depressive reaction is surprisingly high in all areas of medical practice. It is believed to be chiefly responsible for the difficult "psychosomatic" problems which are the "headaches" of medical practice.

The depressive reaction is described as a reaction to a real or imagined emergency situation in which the patient feels overwhelmed. The patient's reaction to this situation constitutes the psychodynamics of depression; an understanding of these psychodynamics enables any doctor to adequately and specifically treat the depressive reaction.

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Discussion (Abstract)

Dr. Joseph B. Parker, Jr., Lexington, Ky. Although we like to think all physicians are aware of the high incidence of depression, sometimes, and as an English physician (Ross) wrote a number of years ago, one may not be aware of the depressive components of his patient's illness until after he has had a suicide. Apparently, many do not always recognize depressions when we note that there are approximately 18,000 to 20,000 suicides a year in our country. And from the studies of Dr. Eli Robins, it is evident that not all psychiatrists as well as physicians are able, even when they recognize the depression, to bring the patient to accept the necessary psychiatric treatment.

Dr. Fulghum rightly has stressed that a depressive mood may manifest itself by irritability, gastrointestinal symptoms or other manifestations that are medically more acceptable.

It has been my impression that it is very difficult to study objectively the antidepressant or psychic energizers. I recall a number of years ago that those who experienced success with the amphetamines had usually used them with outpatients. Those of us who attempted them with inpatients had little success. In other words, if the patient was sufficiently depressed to warrant hospitalization the amphetamines, in our experience, gave him little relief. Also, the nature of the depressions to remit makes it difficult to evaluate the efficaciousness of any mode of therapy. Before the days of electric shock and psychotherapeutic drugs, psychiatrists treated patients 2 to 3 years and in some instances longer, until ultimately the depression lifted.

I would tend to agree in most instances with the psychodynamics and rationale of approach of psychotherapy that Dr. Fulghum has outlined. We should note, however, that investigators, studying older individuals, report depressive episodes related to physical decline and loss of self-esteem without significant underlying hostility. We may see despondency without anger in the individual subjected to recurring episodes of depression as in the manic depressive patients who despair over the prospects that they must again endure an unknown period of depressive agony.

Many times depressive patients can be treated as Dr. Fulghum outlines without either electric shock or psychotherapeutic drugs. If, however, we have empathy with the patient's suffering and a realistic understanding and consideration of his safety and of his economic and social welfare, electric shock, on occasions, may be the humane choice of treatment. When the depression does not remit with the regimen Dr. Fulghum recommends, as pointed out by the late Dr. Lewis Hill, a

psychoanalyst, and Dr. John Patton, electric shock not only can lift the depression but can facilitate the patient's ability to enter effectively into psychotherapy. Our mode of treatment, therefore, as in other fields of medicine, should be determined by what is safe for the patient and what the patient needs at a particular time in the course of his illness to reach an optimum recovery.

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Griseofulvin — A Sixteen Months Study*

THOMAS W. MURRELL, JR., M.D., R. CAMPBELL MANSON, M.D., E. RANDOLPH TRICE, M.D., and MILES E. HENCH, Ph.D.,† *Richmond, Va.*

The effectiveness of an antibiotic orally upon fungal infection of the skin was an amazing demonstration. Though "cure" is not universal, control of infection is usual. Relapse is impossible to differentiate at present from reinfection.

SINCE THE INITIAL CASE REPORTS by Blank[1] in 1958, upon the use of griseofulvin in the treatment of superficial fungal infections of the skin, numerous papers and symposia have been published on the subject. Most of this work has indicated that for the first time an oral antibiotic is available which has definite effect on the growth of certain superficial fungal infections in man, presumably due to the ability of some product of the drug to bind itself to keratin and thereby interfere with certain nutritional requirements of these organisms.

The purpose of this study was to evaluate the effectiveness of griseofulvin in the treatment of fungal infections due to *Microsporum audouini* and *Trichophyton rubrum*.

Method

Patients selected for this study had positive cultures for *Microsporum audouini* and *Trichophyton rubrum*. Photographs were taken initially of all patients with *Trichophyton rubrum* infections, and subsequent photographs were taken to record the course of therapy. Early in the study complete blood counts were done initially followed by white blood counts at bimonthly intervals. This procedure was abandoned after 6 months since no cases of persistent leukopenia were encountered. None of the patients in this study received any type of local treatment.

Microsporum Audouini Infection of the Scalp.

Thirty children ranging in age from 5 to 12 years were selected for pilot studies. Cultures were taken before therapy was begun and the Wood's light used to evaluate results. Twenty-five patients were cured in from 5 to 8 weeks by administering griseofulvin by mouth in dosages based to body weight, i.e., 500 mg. per day for children under 50 pounds in weight, 750 mg. per day for patients 50 to 100 pounds and 1,000 mg. per day in patients 100 pounds and over. Further studies of 15 patients indicated that griseofulvin given in the amount of 1 Gm. every 8 hours for three doses resulted in cures in 6 weeks regardless of age or weight. This schedule had merit also since patients had no nausea or other gastrointestinal difficulties which were feared in "loading" doses considered for children weighing 60 pounds and under.

Following these pilot studies an epidemic of tinea capitis due to *M. audouini*[2] in 23 negro schools was undertaken for treatment. Each child having a positive result with the Wood's lamp was cultured at the school. Subsequently all children with positive cultures of *M. audouini* were re-examined by us under the Wood's lamp and 1 Gm. of griseofulvin given by mouth at the school. Each patient was instructed to take an additional gram in 8 and 16 hours. The patients were instructed to cut the hair down to one-eighth inch in length in 2 weeks and at 4 weeks. Each patient was re-examined in approximately 6 weeks.

Of 430 patients, which included 373 boys and 57 girls with an average age of 7.8 years, 404 were cured in six weeks and 24 were failures. The cure rate with the 3 Gm. of griseofulvin in divided doses in 24 hours was 94 per cent (Table 1).

Trichophyton Rubrum Infections.

Ninety-five patients with *T. rubrum* infec-

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This study was made possible by a grant from the A. D. Williams Fund, Medical College of Virginia, and the Schering Corporation, who supplied griseofulvin as Fulvicin.

TABLE 1

M. AUDOUINI INFECTION OF THE SCALP

Sex	*Number*	*Average Age*
Male	373	
Female	57	7.8 yrs.
Total	430	
Griseofulvin Gm. 3 in 24 hours (Gm. 1 every 8 hrs.)		
Cured	404	94%
Failures	24	

tions of the skin have been under observation during the past 18 months. Although a number of these patients had involvement of multiple areas of the body, for simplicity the results are reported according to various regions of the body. All patients received griseofulvin 250 mg. by mouth after meals and at bedtime (1 Gm. per day). Estimates of cure were based on clinical observation, negative cultures and 3 to 6 months follow-up.

Trichophyton rubrum infection of the palms. Twenty-eight patients were treated for *T. rubrum* infection of the palms. There were 25 men with an average age of 42, who had been infected for an average of 13.6 years. Three women with an average age of 45 had the disease for an average of 18 years. Of these patients, 5 have apparently been cured of the infection, a total of 17.8 per cent (Table 2).

An analysis of the 5 cured patients reveals a considerable variation of cure in relation to duration of the disease and length of treatment. The woman in this group had been infected for 14 years and required 16 weeks of treatment, while one man had had the disease for the same length of time and required 40 weeks of therapy for cure. It may also be noted that 2 patients of this group who had had the disease for 32 and 30 years were cured in 32 and 24 weeks which is less than that required for the patient who had had the disease half as long (Table 3).

TABLE 2

T. RUBRUM INFECTION OF THE PALMS

Sex	*Number*	*Average Age*	*Avg. Duration In Years*
Male	25	42	13.6
Female	3	45	18
Total	28		
Griseofulvin *per os* 1 Gm. day Patients Cured 17.8%			
Male	4		
Female	1		
Follow-up—3 and 6 months			

TABLE 3

T. RUBRUM INFECTION OF THE PALMS

Patients Cured Griseofulvin 1 Gm. Day

Sex	*Age*	*Duration Disease*	*Treatment In Weeks*
Female	44	14 yrs.	16
Male	13	6 mos.	14
Male	50	32 yrs.	32
Male	52	30 yrs.	24
Male	35	14 yrs.	40

An analysis of the 19 patients who have been failures up to the present time revealed that 5 of the patients had been on the drug for 50 to 60 weeks and 5 others for 40 to 50 weeks. These 10 patients have been treated longer than any in the cured group (Table 4).

It is apparent that in the treatment of *T. rubrum* of the palms it is impossible to predict the length of time for cure based on duration of the disease or even the time required to cure a patient with infections of equal duration.

Trichophyton rubrum infection of fingernails. Thirty-eight patients with *T. rubrum* infection of the fingernails were treated. There were 35 men, averaging 43.5 years in age, who had had the disease for an average of 12.4 years. In addition there were 3 women whose average age was 55 years and who had been infected for an average of 17 years. Of these patients 18 were cured or 47.5 per cent (Table 5).

The 18 patients cured of *T. rubrum* infection of the fingernails were cured in an average of 22 weeks. However, it should be noted that 10 patients who failed to respond had received treatment for an average of 35 weeks. There was no relationship in this group between the length of time required for cure and duration of the disease (Table 6).

It is apparent from the aforementioned data that it is not possible to predict the length of time required for treatment of *T. rubrum* infection of the fingernails.

TABLE 4

T. RUBRUM INFECTION OF PALMS

Treatment Failures Griseofulvin 1 Gm. Day

Patients	*Duration Treatment In Weeks*
5	50-60
5	40-50
4	30-40
5	Under 40

TABLE 5

T. RUBRUM INFECTION OF FINGERNAILS

Sex	*Number*	*Average Age*	*Avg. Duration In Years*
Male	35	43.5	12.4
Female	3	55	17
Total	38		
	Griseofulvin *per os* 1 Gm. Day Patients cured 47.5%		
Male	16		
Female	2		

We have observed a change in the nails of 2 patients which may be of significance; each was believed cured in approximately five months. Six months later both patients noticed separation of a nail beginning at the tip unaccompanied by any subungual scaling, inflammation or history of trauma. Cultures from these areas of lysis were negative for *T. rubrum*. We are not yet sure if these patients represent true relapse or whether the new nail tends to separate from the nail bed from slight injury.

Trichophyton rubrum infection of toenails. Thirty-three patients were treated for *T. rubrum* infection of the toenails. In this group are included 19 men averaging 49.5 years of age who had had the disease an average of 17.8 years. There were 14 women whose average age was 35.7 years who had the disease for an average of 11.8 years. Three (8.8%) of these patients have been cured (Table 7).

Analysis of the cured patients reveals that there were 2 women (identical twins) who had been infected with *T. rubrum* for three and one years which was considerably less than the average of the rest of the patients in the group. The man who was cured had very mild involvement (Table 8).

A review of the patients who have not responded to treatment indicates there were 7 patients who had received treatment for 50 to 70 weeks and 15 from 24 to 50 weeks (Table 9).

TABLE 6

T. RUBRUM INFECTION OF FINGERNAILS

Patients	*Treatment Successful Griseofulvin 1 Gm. Day Duration*	*Average Treatment In Weeks*
18		22
	Treatment Failures	
10		35
10		16
38 Total		

TABLE 7

T. RUBRUM INFECTION OF TOENAILS

Sex	*Number*	*Average Age*	*Avg. Duration In Years*
Male	19	49.5	17.8
Female	14	35.7	11.8
Total	33		
	Griseofulvin *per os* 1 Gm. Day Patients cured 8.8%		
Male	1		
Female	2		

Trichophyton rubrum infection of the soles. Twenty patients have been under treatment during the period of this study for *T. rubrum* infection of the soles. We are unable to present any data of significance relating to these patients since the majority are still on griseofulvin because of involvement of toenails. A number of these patients have shown improvement or clearing while taking the drug.

Trichophyton rubrum infection of glabrous skin. Fifteen patients were treated for *T. rubrum* infection of the glabrous skin. Due to difficulties in follow-up we are unable to present any data of possible significance. The rapid clearing of lesions of the glabrous skin in two to six weeks was as beneficial as it was dramatic. Two of the patients in this group were brothers who were 48 and 50 years of age and had had the disease constantly for over 30 years. These patients had received every known local treatment for the disease, which in each involved to some degree every area of the body except the face and scalp. While these patients took griseofulvin 1 Gm. a day for an average of 40 weeks because of involvement of the nails, the glabrous skin lesions disappeared in 4 weeks and have not re-occurred 8 months after therapy has been discontinued.

TABLE 8

T. RUBRUM INFECTION OF TOENAILS

Sex	*Age*	*Duration Disease*	*Treatment Successful Griseofulvin 1 Gm. Day Treatment In Weeks*
Female	27	3 yrs.	56
Female	27	1 yr.	32
Male	38	13 yrs.*	16

*Mild Involvement

TABLE 9

T. RUBRUM INFECTION OF TOENAILS

Patients	*Treatment Failures Griseofulvin 1 Gm. Day Duration Treatment In Weeks*
7	50-70
15	24-50
6	Less than 24

Reactions to Griseofulvin

Among 470 patients receiving relatively short-term therapy for *M. audouini* infection of the scalp no reactions to the drug were noted. Among the 95 patients on long-term therapy, only 3 had complications necessitating discontinuance of the drug. There was one case of headache (present at any level of dosage), one of urticaria and one patient in whom a severe abscess developed in the distal space of one finger which necessitated partial amputation. The significance of the complication in this patient was open to considerable question. Although the patient had been infected with *T. rubrum* of one hand for 35 years, no similar type of bacterial infection had occurred except when on griseofulvin.

There were 17 patients who developed transient reactions which temporarily interfered with treatment (Table 10). The 3 instances of transient leukopenia returned to normal although the drug was continued at 1 Gm. per day.

Discussion

The use of griseofulvin in the treatment of infection of the scalp by *Microsporum audouini* is unquestionably curative. The results obtained in treated *Trichophyton rubrum* infections of glabrous skin are apparently excellent. As may be said for all infections with *T. rubrum,* only time will answer questions relating to relapse and reinfection.

The results obtained in treating fingernails infected with *T. rubrum* with griseofulvin are very encouraging. While the cure rate in this study is up to the present time only 47.5%, it is anticipated that a larger number in the group will eventually clear. Without question, griseofulvin has apparently cured more *T. rubrum* infections of nails than any known previous forms of therapy.

TABLE 10

REACTIONS TO GRISEOFULVIN

Long-Term Therapy Number of Patients 95 Sufficient to Stop Drug			
Headache			1
Distal Space Abscess Finger			1
Urticaria			1
Transient			
Headache	3	Nausea	1
Diarrhea	4	Leukopenia	3
Night Sweats	1	"Id" Reaction	5

As previously stated we do not have sufficient data to evaluate the effect of griseofulvin in the treatment of *T. rubrum* infection of the soles and glabrous skin.

The results obtained in this study in the treatment of infection of toenails by *T. rubrum* are very poor up to this time. While a number of reasons may be postulated for these results, the rate of growth of toenails, the frequent severity of involvment and the increased temperature of skin and nails associated with wearing shoes may play a part.

Well-controlled studies are needed to determine whether the use of keratolytics and fungistatic agents used locally in combination with internal griseofulvin results in higher rates of cure.

Studies relating to variations in hydration and dehydration of keratinizating cells of the epidermis in patients taking griseofulvin may result in valuable information.

While griseofulvin has by no means solved the problem of *T. rubrum* infections in man, the discovery of the drug has resulted in a great advance in the treatment of this disease.

Summary

1. The results in the treatment of 470 patients with *Microsporum audouini* infections of the scalp with griseofulvin are reported.

2. The use of griseofulvin in the treatment of 95 patients with *Trichophyton rubrum* infections of skin and nails has been reported.

References

1. Blank, H., and Roth, F. J.: The Treatment of Dermatomycoses with Orally Administered Griseofulvin, A.M.A. Arch. Dermat. 79:259, 1959.
2. Murrell, T. W., Jr., Manson, R. C., and Trice, E. R.: Tinea Capitis in a Public School System—Control with Griseofulvin, Virginia M. Month. 88:4, 1961.

Discussion (Abstract)

Dr. Henry W. Jolly, Jr., Baton Rouge, La. I think the essayist and his collaborators should be commended for their timely and excellent analysis of one of the newer drugs in our armamentarium.

It is a unique experience to witness from the outset the clinical use of a new drug. We may be observing

more than just the use of a new drug, for it may well be that this is the beginning of a new family of drugs and that griseofulvin *per se* is but the original member. It is conceivable that chemical and biologic variants of griseofulvin will follow in the same manner that the so-called "mycin" drugs followed in the wake of penicillin.

On the other side of the ledger, again thinking back to the early days of penicillin and other antibiotics, all of the side effects may not be clarified as yet, and we should certainly keep our clinical and laboratory "eyes" alert for not only those that have already been mentioned but for new ones as yet unrecognized. I am not inferring that diabetes is a side effect or complication of this therapy, but I do recall two patients who obviously were not responding well to griseofulvin and, in face of a negative urinalysis, were found to have a diabetic glucose tolerance curve. Rearing its ugly head is the possibility of resistance of organisms to the drug. Strains of fungi, a concept not greatly discussed heretofore, may exist with varying resistance. These factors, along with host resistance or lack thereof, may help to explain in part why the authors found such a variance of time required to clear clinically identical infections.

The authors' paper deals primarily with the clinical side of the picture in which we are most interested at the present time. Their experience in tinea capitis seems in general to agree with observations by most people with whom I have talked. However, it has been my personal experience that many of these patients have had to be treated ultimately with daily doses over a period of several weeks or months when the initial massive dosage did not effect a clinical cure. Doses of 0.5 Gm. per day or less have been found ineffectual, regardless of the weight of the child. Whichever schedule one uses seems unimportant, when one realizes that we have at hand a drug now which will obviously cure the overwhelming majority of cases of tinea capitis. Gone, forever, we hope, are the days of x-ray epilation of the scalp and tedious home treatment which I am sure frayed the nerves of both the parents and the child.

Infections of the glabrous skin by *T. rubrum* have likewise done well in my experience. It is particularly gratifying to clear one of these cases of 10, 20 or even 30 years duration in a few weeks, when all previous treatments over months and years have failed to produce anywhere near the results we see with this drug.

As has been brought out so well in the paper, the nails, particularly the toenails and the feet, particularly the spaces between the toes, present our greatest problem with this drug today. I, too, have been using this drug for 16 months for, knowing of its impending release, I did not treat any cases of chronic fungal disease during the summer of 1959, but postponed them for the availability of griseofulvin. Unfortunately, I must admit that I do not believe I have seen any cases of onychomycosis of the toenails cured to date, and I too have had some of these cases under active treatment for 16 months. I believe I have had several instances of infection of fingernails cleared, but like the authors, at the present time I am not willing to use the word cure. I do not think that we should let these cases discourage us. Certainly the drug helps in these cases, probably more so than anything we have had before.

The really greatest drawback to this drug is the matter of reinfection. We are all familiar with the fact that contact with the organism alone is not the key to infection, for certainly we have seen many people chronically exposed to these organisms who never develop clinical disease. Therefore there must be some element of individual susceptibility, lack of immunity or whatever we wish to call it that plays a major role in determining whether a person will or will not develop fungal infection. The use of this drug does not alter the person's immunologic reactivity. Therefore we must realize that when we cure a disease caused by a fungus with this drug we are merely curing the present infection but are not doing anything to prevent a reinfection. Of course recurrences are due to discontinuing the drug too rapidly but this is a different problem.

In closing allow me to again commend the authors for a very good presentation.

Dr. John H. Lamb, Oklahoma City, Okla. I, too, enjoyed this presentation on griseofulvin. It has been the best antifungal drug yet found.

As you know, for several years we have been interested in pregnenalone, an early steroid, because of its antifungal properties for cultures of *T. rubrum*. We have found it very useful in severe cases of *T. rubrum* infection. The skin lesions were entirely cleared after several months on 400 mg. daily, but we were never able to influence the infection of either the fingernails or the toenails.

I have taken griseofulvin, for my *T. rubrum* infection of 30 years duration. I started in January 1959 and continued it until August of that year, taking 2 Gm. daily for 2 months and then reduced the dose to 1 Gm. daily. The skin of my feet showed psoriasiform lesions, but in one month it was entirely clear; in 7 months my onychomycosis of the toenails had cleared 90 per cent.

After 14 months without the drug I am now slowly getting a recurrence in two of my toenails. I would say it is a 40% recurrence; my feet have a 100% recurrence. I have been interested in this drug as a light sensitizer, and after I was on the drug for 4 months I went on a three day fishing trip and developed an unusually severe sunburn on my legs and hands to which A-Fil did not protect me. On my return home I tested myself with cold quartz radiation unfiltered and found I had a pathologic sunburn reaction to 4 E. D. We had a second patient who on griseofulvin became sensitive to light and had a similar pathologic sunburn reaction to the same dose of cold quartz radiation. We tested 18 other patients on griseofulvin to ultraviolet unfiltered and through window glass. Four patients showed a positive erythematous reaction to cold quartz through window glass which would represent from 3,200 angstroms to 3,400 angstroms. This reaction is not found in normal individuals and thus they are mild reactions. We should tell our patients while on griseofulvin to stay out of intense sunlight. Declomycin, an excellent tetracycline with a chlorine radical also is a light sensitizer. It is worse than griseofulvin and patients on this medication must also stay out of intense sunlight. These drugs should be given with caution to patients with polymorphic light eruption and lupus erythematosus.

A Few Remarks on Physical Medicine, Rehabilitation and Orthopedic Surgery*

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The author analyzes the inter-relationships of physical medicine, rehabilitation and orthopedic surgery. The orthopedic surgeon actually fathered the specialty of physical medicine and rehabilitation, since he used physical methods in the treatment of patients having musculoskeletal disease years before physical medicine and rehabilitation became a specialty.

TO SOME OF YOU HERE it may seem presumptuous that an orthopedic surgeon should discuss some of the "why's" and "wherefore's" of a sister specialty in relation to his own. I can assure you that this is only being done on invitation of your Chairman, whom I have known and worked with for many years, and with whom I have had many serious discussions concerning rehabilitation and physical medicine and its relationship to orthopedic surgery.

In the latter months of World War II and in the immediate post-war years, I had the pleasure of serving on three of the subcommittees of the Baruch Committee on Physical Medicine, working with Frank H. Krusen, Howard A. Rusk, George G. Deaver, and many others who laid foundation stones for the specialty of physical medicine and rehabilitation as it is practiced today, or what by some is spoken of as "Physiatry." During part of World War II, I served in the Office of the Air Surgeon and acted as an orthopedic advisor to Howard Rusk in developing the Air Force program of rehabilitation. Since the War I have been deeply interested in what has been happening in the development of rehabilitation facilities and services. I have given many talks and written several papers on rehabilitation, and through my activities with the Nemours Foundation have had much to do with planning and developing rehabilitation programs in many of the Southern states. I should mention that since 1949, as Medical Director of this Foundation, I have helped to arrange for 59 Foundation-sponsored conferences in 15 Southern states concerned with different phases of rehabilitation of handicapped children. These are a few of my qualifications for this talk in addition to being an orthopedic surgeon.

What I shall say, which because of time will have to be short and will in no way be as full a discussion as it should be, might be likened to the teachings of Hippocrates, who probably was the first physician to be deeply concerned with the modalities of physical therapy and the philosophy of comprehensive rehabilitation. It is said that the basis for his teachings, simply stated, was: "Look, then think." I shall take a "look" at orthopedic surgery and some of its present-day practices, a "look" at what the specialty of physical medicine and rehabilitation is and is doing, and then shall "think" and, of necessity, will "think" out loud for the benefit of you, the audience.

In the beginning of a discussion of this kind, the premise should be stated that the basic reason for a person being a physician is "to make sick people well." How this can best be done should be the first concern of every physician no matter in what field of medicine he is practicing. If this premise is admitted, then how do physical medicine, rehabilitation and orthopedic surgery relate to each other for the good of the patient? First, what is physical medicine and rehabilitation? According to the writings of Krusen[1,2] and what is published in the *Archives of Physical Medicine and Rehabilitation,* physical medicine and rehabilitation should be defined as that branch of medicine concerned first with the diagnosis and management of, and research on diseases and disorders of the body by means of (1) physical agents, such as light, heat, cold, water and electricity; (2) mechanical devices; (3) manip-

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ulation; (4) massage and (5) exercise; and second with total rehabilitation or the physical, mental, social and vocational restoration of the patient to the fullest extent compatible with his abilities. Next, what is orthopedic surgery? The latest definition as approved by the American Academy of Orthopedic Surgeons in January 1960 is: "Orthopedic surgery is a medical specialty that includes the investigation, preservation, restoration and development of the form and function of the extremities, spine, and associated structures by medical, surgical and physical methods." You will note that the first mentions physical agents and the second physical methods, which are in reality one and the same thing, but, unfortunately, there is nothing in the definition of orthopedic surgery to suggest the interest the specialty should have in the total rehabilitation of its patients. Your Chairman, Dr. Park, last year in his address[3] before this Section, stated: "Physical medicine and rehabilitation is the specialty concerned with the diagnosis and medical management of disorders of motion and locomotion." He enumerated the various conditions treated by himself as a specialist in this field as follows: arthritis, neuritis, spinal cord injury, amputation, the convalescent stage of hemiplegia, cerebral palsy, poliomyelitis and other musculoskeletal disorders. These are all conditions which over the years have been referred to, and treated by the orthopedic surgeon.

Let us first take a "look" at what has happened in orthopedic surgery in the last 50 years. Why is the physiatrist now treating so many orthopedic conditions? With the great advances in operative surgery, orthopedic surgeons, whose practices were formerly largely those of physical medicine and rehabilitation as it is practiced today, have become in many communities primarily operative surgeons; they have been more interested in surgical and mechanical aspects of their specialty than in the many nonoperative and nonmechanical phases. This has been a gradual evolution from the practices of the past, at which time most of the orthopedic treatment was nonsurgical, and before the turn of the century orthopedists were sometimes facetiously referred to as the "buckle and strap" doctors. This recent emphasis on surgery undoubtedly has occurred because of the modern day thinking that for a surgeon to be a surgeon he must use a knife and "cut," i.e., he must do open surgery, and because one full year of the training of the young orthopedic surgeon must be spent on a general surgery service in learning surgical technics, a very necessary requirement for a surgical specialist. In contrast to the emphasis on surgery, it is interesting to note that Philip Wiles,[4] a distinguished orthopedic surgeon of London, wrote in 1952: "However important surgery may be now, it should be the aim of all doctors, including surgeons, to limit and ultimately abolish it." I am sure that very few of the younger men in our specialty have realized that there is this type of thinking among some of their elder statesmen.

For the orthopedic surgeon "to make orthopedically sick people well" and to accomplish this most effectively, the orthopedic surgeon must employ treatment by the physical means of heat, light, massage, hydrotherapy, and electricity; he must teach special exercises and activities of daily living and, furthermore, he must do whatever is necessary for the restoration of the patient to maximum function and usefulness at home and in employment, using all forms of therapy now used by the specialist in physical medicine and rehabilitation. Perhaps orthopedic surgery should be called orthopedic medicine and we should be orthopedic physicians, as suggested by Dr. Arthur Steindler[5] and mentioned in your Chairman's address last year. On the other hand, perhaps there should be two types of orthopedists—one a medical orthopedist and the other a surgical orthopedist. If the large incidence of orthopedic patients requiring nonoperative treatment is considered, certainly we orthopedists should be much more interested than we are today in all of the modalities of physical medicine and the programs of comprehensive rehabilitation. What has happened in recent years is that in many instances, due to the pressure of large clinical practices and the lack of time, there has been a tremendous amount of apathy on the part of the average orthopedic surgeon toward a complete follow-through in the care of his patients, whether primarily surgical or nonsurgical. In many communities orthopedic surgeons now are becoming aware of the fact that the specialty of physical medicine and rehabilitation is beginning to care for more and more of the patients who in the past have come to the office and

clinic of the orthopedic surgeon. Some orthopedic surgeons have been disturbed by what has been happening, not fully realizing that it has been primarily due to the shortcoming and failure of the orthopedic specialty as a whole to take the leadership since World War II in developing programs of total rehabilitation which includes physical medicine.[6]

Now a word about the origins of the specialty of physical medicine and rehabilitation. During the early war years the Armed Forces suddenly realized that they were faced with a problem of returning to duty thousands of sick and wounded soldiers and sailors in minimum time, so necessary in order to meet their manpower shortages. We who were in the Armed Forces Medical Services soon realized that for the best job to be done there would have to be full-time physicians devoted to the direction of programs of total rehabilitation. The few specialists in physical medicine in the Medical Services at that time knew little about technics for rehabilitation. A few of the civilian orthopedic surgeons in the Armed Forces, such as Henry Kessler, had long been concerned with programs of rehabilitation in their home communities. So what happened was that programs for the training of physicians in rehabilitation were established along with the opening of special hospitals for convalescent care and rehabilitation. This was in many ways comparable to what had happened in the first World War with the shortage of orthopedic surgeons, when special training centers were set up by the Army for orthopedic instruction in the AEF in France as well as in the United States. Howard Rusk took the lead early in the thinking and planning for rehabilitation services in World War II and showed what could be done in the Army Air Force. The Medical Services of the Army and the Navy soon followed suit. The programs of rehabilitation which followed this start constituted one of the greatest advances in medicine of modern times. Some have said that no similar effort in medicine has ever achieved so great a degree of success in so short a period of time. This is a true statement. At the end of the War many of the physicians in the programs of rehabilitation who were truly dedicated to the work they had been doing in the services wanted to continue in this field of medicine in civilian practice. It was in this period that, largely due to the efforts of Frank Krusen and Howard Rusk, rehabilitation was linked with physical medicine and the new specialty was established. In 1954, I[7] made the following statement: "The joining up of these two branches of medicine came about as a 'marriage of convenience' after the last War. Due to the extensive and excellent programs of rehabilitation in the Armed Forces, there were at that time hard and distinct growing pains in this field of medicine in both civilian and military practice. However, the physicians limiting their work to rehabilitation were few and, in reality, rehabilitation was a medical stepchild with no allegiance. Rehabilitation then was not ready to stand on its own feet and have an independent position, so physical medicine 'took it under its wing.'"

At this time the words *physiatry* and *physiatrist* came into use; *physiatry* is not a word which applies to this whole field of medicine as now practiced. *Physiatrist* means "a healer by physical agents" and does not include the social, educational, and vocational aspects of rehabilitation, nor does it include medical care except that given by physical means. However, in the last decade, *physiatry,* as a word, has come to be synonymous with physical medicine and rehabilitation in the minds of the profession. Those who had been in rehabilitation in the Armed Forces and carried their work over into civilian practice formed the founding member group of this new specialty. It is my opinion now, as well as at the end of the last War, that if rehabilitation was to be given a place in medical practice it would have been better not to have combined it with physical medicine. Physical medicine as such constitutes only one part of rehabilitation. The many other parts are far more important in the over-all picture. I am sure that one of the reasons why rehabilitation has not developed faster since World War II is because it has been linked in name with physical medicine. Physical medicine *per se*—not what it has developed into today—is a form of treatment. Its modalities may be used at different times by nearly all fields of medicine. It does not set itself apart as a specialty involving the care of one system or group of parts of the body as most specialties do which render treatment. If rehabilitation were separated from physical medicine, the physician limiting his

work to rehabilitation then would be a rehabilitation physician, a name which describes what he really is far better than the word *physiatrist*.

Soon after the War the Armed Forces and Veterans Administration Medical Services, realizing the tremendous value of properly administered rehabilitation programs, established physical medicine and rehabilitation services in their hospitals. Many predicted at this time that there would be a very rapid growth of this new specialty, but such questions must now be asked 15 years later as: "Has this growth taken place?" "Has the specialty the appeal to attract a sufficient number of young physicians to do the job?" "To what extent has physical medicine and rehabilitation become established as a medical specialty in the minds of all physicians and the public?" "Is it a true specialty or is it not, as has been said, a piecing together of parts from many different phases of medicine into an insecure whole?" Some of what is implied in these questions was discussed by the Chairman of this section last year, giving good and valid reasons for such based on his own experiences.[3] I will not attempt to give you the answers, since I think each one of you interested in this field of medicine should think about what has happened and answer for yourself. It is true that the specialty has not attracted as many physicians for training as it had once hoped to; it is particularly alarming to me to see the number of unfilled positions for physician directors in rehabilitation programs and centers. Your Chairman has said that the physiatrist in the rehabilitation center is now serving as a medical planner and coordinator of physician, paramedical, vocational training and social service activities. He is seeing that the patient receives the attention of all indicated disciplines and social services. This is definitely making him an administrator of patient care rather than a physician on a one-to-one basis in the care of the patients. Perhaps he is, as Wright has said,[8] "the 'managing physician' considering the 'whole' person." Perhaps this is all he can possibly be in most medical centers and communities with the present short supply of physiatrists. This in itself may be a discouraging factor to the young man who might be interested in the specialty and wants to work with "sick people."

Unfortunately, as time has gone on, a few of the younger physiatrists and their practices have become upsetting to some orthopedic surgeons, largely due to conflict in opinion on patient care, undiplomatic remarks and because in some of the government institutions all prescriptions for the treatment of orthopedic patients by physical methods and rehabilitation technics must be given by the physiatrist. This latter is a rule which is fundamentally wrong if the orthopedist is to continue to "make his own sick people well" and be responsible for their return to normal. As it is now it is a division of responsibility with the patient caught in the middle and oftentimes *not* for his good. In analyzing the scope of both practices, it may be realized that such a conflict would take place sooner or later, since both specialties are involved in making many of the same types of "sick people well." To clarify the situation two questions should now be asked and frankly discussed: First, which specialty is best qualified to do the job, and second, are the best qualified specialists doing the best job which can be done? To answer the latter first, it can only be said that "time will tell." In answer to the first question, it must be said that perhaps the orthopedic surgeon might be theoretically the best qualified to treat musculoskeletal disorders but, in reality, it may be that the individual physiatrist, manifesting greater interest in certain conditions, such as hemiplegia and paraplegia, is accomplishing more than the orthopedist is with patients having comparable conditions. The time has now come when there should be discussions between the leaders of both specialties concerning patient care, and which specialty should focus attention on what conditions for the good of the patient. Several years ago the American Medical Association established at the annual A.M.A. meeting a Joint Session on Physical Medicine and Rehabilitation, in which both specialties could discuss together common problems for mutual advantage. This, I am sure, has done good, but this one session a year with its published papers is not reaching enough members of the two specialties to make a great deal of difference in thinking. The poor relationship between physiatry and orthopedic surgery in many communities is regrettable, and should not be so long as we both are living and working together.

I am not prepared to say with documented knowledge what the relationship between physiatry and other fields of medicine is. However, it would be my opinion that primarily due to the small number of physiatrists, a

very poor "selling" job has been done *to the profession* as a whole, and most of the general practitioners do not yet know what the specialty is and what it can do for their patients. On the other hand, the selling job of rehabilitation by the physiatrists and others *to the public* has been excellent and this public has become tremendously interested. Many lay boards of hospitals and other medical institutions have insisted upon rehabilitation services being established, knowing the tremendous value to their patients and the financial saving to the institutions which such well-organized services can be. This has been done oftentimes with almost complete apathy on the part of the physicians responsible for establishing such services. In the United States, I am told, there are now approximately 150 complete rehabilitation centers and 150 others offering some types of rehabilitation services. However, with the short supply of physiatrists and the lack of interest of so many orthopedic surgeons, many of these institutional services and centers I am sure are not receiving proper medical direction and supervision, and many very little at all. A serious "look" must be taken by all physicians into this situation. Particularly must this "look" be taken by the orthopedic surgeon who, in his practice, has the largest number of patients in need of rehabilitation. The statement was made several years ago by one of our leaders, "How futile would be all of our treatment, particularly our surgery, without proper after-care and how dependent we are on effective rehabilitation for our patient." But rehabilitation goes far beyond our two specialties, for all physicians are responsible, even though the physiatrists and orthopedic surgeons are the ones to whom people are looking to give the strong and vigorous leadership so needed for the success of the program.

In 1948, at an International Rehabilitation Congress in Mexico City, I[9] stated, "There is an immense job of education needed for the physicians and laity before rehabilitation will be integrated into the everyday practice of medicine." During the intervening 12 years some education has been done, but rehabilitation is far from being integrated into the everyday practice of the average physician. In 1954, at a meeting of the International Society for the Welfare of Cripples in The Hague, I[7] made the statement that there must be "full participation in rehabilitation by all physicians" and that rehabilitation must be given "an independent status in medical practice." I suggested that leaders from all fields of medicine should come together to discuss how this can be done and that a Rehabilitation Council of Physicians, representing all branches of medicine, should be established on a national level. The duties of this Council should include setting the policies for the profession and seeing that physicians in each field of medicine take the responsibility for incorporating good and better programs of rehabilitation in their teaching and practices. Perhaps a start has been made by the A.M.A. Council on Rehabilitation, but certainly the "ball is not rolling" very fast.

Since rehabilitation is the responsibility of every physician, more and more physicians must become not only interested but also actively participate in programs if progress is to be made as it should. Every practitioner must be convinced that after medical care it is his duty to see that the necessary rehabilitation of his patients is carried out and, furthermore, he must know what good total after-care consists of. Rehabilitation should be taught to be, and always thought of as, a necessity in treatment, even as much as roentgenographic and laboratory examinations. If this work is to be done, it cannot be left only to the physiatrist—their numbers are too small. The leaders in every field of medicine, and particularly orthopedics, must become more involved than they ever have in the past. If they do not, they are failing in their duty to the public.

Now a word concerning what Dr. Park has stated physiatry should include. If the physiatrist is to treat only the abnormalities of motion and locomotion as he has mentioned, is not he practicing orthopedic surgery? If the treatment of these conditions is to constitute the major practice of the physiatrist, he should have more training in orthopedics than he is now receiving. In fact would it not be desirable for the physiatrist to have at least 2 years of orthopedic training before going into the specialty? Both specialties should, by all means, have the same fundamental training in the treatment of all musculoskeletal diseases, including the same training in prosthetics and orthotics. The patients of the physiatrist cannot be given the best possible medical care unless such occurs. All of the present practices of physical medicine related to the treatment of

abnormalities of the musculoskeletal system fall within the scope of treatment by the orthopedic surgeon. If the patients having musculoskeletal disease are removed from the practice of the average physiatrist, there are not many patients left for him to treat; however, there is ample work for him to do in the direction of rehabilitation centers and services for which he is well qualified by training and experience. If our two fields of medicine so closely allied in so many practices continue to treat so many of the same conditions, perhaps some consideration should be given to the amalgamation of the two specialties, for there is certainly a great deal of duplication in what we are now doing. If not an amalgamation, there should be a much closer alliance than that which exists today. If we continue as we are, there are bound to be continuing conflicts, and the public, to which we look for support, will become more confused than they are now about medical care. In many ways the only difference today between the practices of many physiatrists and orthopedists is that the orthopedist does open surgery and fractures and the physiatrist does not.

In this type of discussion mention should be made of the relationship between physiatry and the therapies,—occupational and physical. This is relatively new and in many places the relationship is strained. Many physiatrists feel, and statements have been made, that they should direct the teaching in the schools of physical therapy and occupational therapy, since these therapies involve treatment by physical means, but the orthopedist also treats by physical means. He was treating by physical means long before physiatry as a specialty was thought of. These paramedical specialties were developed originally by orthopedic surgeons so they might better "make their patients well." Many of the therapy schools now strongly object to being directed by physiatrists; their satisfactory experiences over the years with orthopedic surgeons who helped to establish and develop their schools make them unwilling to accept other direction, which is certainly understandable.

Time is too short to go into a full discussion of the ramifications of this whole problem, which I would very much like to do. What I have given you are only a few rambling, and I am afraid, disconnected thoughts concerned with the "look" and the "think" of Hippocrates, which you may or may not agree with. However, in conclusion, I wish to say that I feel very strongly that the orthopedist needs the help of the physiatrist, or who should more properly be called a rehabilitation physician; he needs this specialist, particularly to promote and assist in the developing of programs of rehabilitation so necessary for the total care of his patients. Without his help in the last 15 years, orthopedic surgery would have suffered.

Dr. Robert B. Osgood,[10] of Boston, said several years ago: "Specialism is rife in these times. Its dangers and its faults demand the attention of all practitioners. The vital integral relation of the part to the whole needs constant emphasis. Exclusiveness and separation need to be condemned. Close association, team play, and commonalty of ethics need to be encouraged." Is not this what is now needed between orthopedics and physical medicine and rehabilitation? We cannot be exclusive and separate from each other, we must have a close association and team play. The leaders in both specialties must create a joint vigorous driving force for progress if we are going to give the service to the patient he expects and rightfully deserves and continue "to make sick people well" in the best manner possible.

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Advances in the Surgery for Deafness*

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Much has been heard in recent years about operations to improve hearing in patients deafened as a result of otosclerosis. The author reviews these in light of his own results.

THE PATHOLOGIC CHANGES in the region of the oval window which cause hearing loss were described by Valsalva over 200 years ago. It has been nearly 100 years since Kessel, in 1876, suggested the removal of the fixed stapes as a surgical treatment for otosclerosis. Passow, in 1879, fenestrated the basal turn of the cochlea and covered the fenestra with periosteum. Hearing was improved for a very short time but was eventually totally lost. Infection was the bugbear of all the surgical approaches when they were done through the tympanic membrane. In 1910, Barany[1] approached the problem through the mastoid with fenestration of the posterior canal, and four years later Jenkins[2] made a window in the horizontal canal and covered it with a skin graft. Again the results, though good, were only temporary. Holmgren[3] and Sourdille[4] followed with two-stage operations for fenestration using various substances, mucosa, skin and conjunctiva to cover the fenestra. The problem was to maintain an open fenestra indefinitely.

Since Lempert,[5] in 1935, described his one-stage operation for fenestration of the horizontal canal via the endaural route, the operation has become gradually standardized with minor but important technical changes. Sufficient numbers of operations have been done now to warrant definite conclusions as to, (1) indications, (2) the predictability of the operation, and (3) the permanency of the results. The indications for fenestration must be emphasized because they are somewhat different from those of procedures which followed. In the first place the operation is indicated in cases of bilateral conductive deafness in which there is no apparent nerve involvement, in other words, a loss of hearing by air conduction with normal or near normal bone conduction. Another way of assessing the cochlear function is with the use of speech tests, and we believe that an ear with a discrimination score of 75% or better, using the Rush Hughes recordings, is suitable for fenestration. Mention is made of unilateral deafness only because the theoretical limit of hearing following fenestration of the horizontal canal is about 20 to 25 decibel level for speech. If one ear is normal and a fenestration is done on the other poor ear and it is not brought up to the same level as the normal ear, the patient is not happy.

Fenestration Operations

In 1959, we presented the results of 661 cases of fenestration which had complete follow-up tests.[6] We divided these cases into 3 groups. Operations in group I were done from January 1945 to July 1949, in group II from September 1949 to May 1953, and in group III from May 1953 to July 1956. Table 1 shows the results in terms of hearing levels for speech in these cases. The improvement in results in each of these groups we believe is due to various changes in technic. Between groups I and II we introduced the microscope and the constant irrigation-suction as suggested by Shambaugh.[7] Between groups II and III we changed from using saline as the irrigating fluid to the use of artificial cerebrospinal fluid (Hartmann's solution). It seems that in all these procedures increased familiarity with, and dexterity in the operation made for improvements in results. We have now added a fourth group, 170 patients, operated on between September 1956 and July 1959, who could complete follow-up. Table 2 shows the results. One hundred twelve were original fenestrations and 58 had fenestrations following previously unsuccessful stapes mobilizations. The results in this group are closely comparable to those in group III. The course of these patients has been followed from 1 to 15 years, and we have found that the results at the end of a year re-

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TABLE 1

FENESTRATIONS

Hearing Level (db)	Group I Jan. 1945 to July 1949			Group II Sept. 1949 to May 1953			Group III May 1953 to July 1956		
	No.	Per Cent	Cumulative Per Cent	No.	Per Cent	Cumulative Per Cent	No.	Per Cent	Cumulative Per Cent
20 db or better	6	3.0		28	12.1		64	28.2	
21-25	49	24.6	27.6	68	29.3	41.4	77	32.6	60.8
26-30	61	30.7	58.3	68	29.3	70.7	41	18.1	78.9
31-35	28	14.1	72.4	29	12.5	83.2	27	11.9	90.8
36-40	20	10.0	82.4	15	6.5	89.7	9	4.0	94.8
40 db or worse	35	17.6		24	10.3		12	5.2	
	199			232			230		

main stationary in all subsequent tests. There were closures of the fenestra in all groups: 15% in group I, 2.8% in group II, 3.3% in group III and 2.4% in group IV. In all cases the closure occurred in less than one year after operation. One can conclude from these results that the hearing in otosclerosis can be restored to a serviceable level by fenestration of the horizontal canal in 90% of cases. We must point out that the hearing level for speech of 35 decibels is equivalent to a hearing level of 30 decibels when pure tones are used as tests, and the average of 512, 1024, and 2048 is taken as the threshold for speech.

When Rosen[8] reported his results on mobilization of the stapes in 1955, much enthusiasm for the procedure was evinced throughout the country. Here was an operation, done under local anesthesia, which, whatever the hearing result, at least left the patient with an anatomically normal ear. There was little morbidity following this procedure in contrast with the interminable postoperative care required following fenestration. The patient could swim and could behave as a normal individual. Although there were reports of success in many series varying from an enthusiastic 80% to a more conservative 50%, it was soon found that there was no way of predicting whether the stapes could, in fact, be mobilized nor whether, if it could be mobilized, it would remain mobile. Our own experience with this procedure is shown in table 3. Again, practice led to improved results. These results,

TABLE 2

H. L. Speech(db)	Fenestration Only			Fenestration After Stapes Mobilization			Fen & Stapes Mobilization Fenestration Total		
	No.	Per Cent	Cumulative Per Cent	No.	Per Cent	Cumulative Per Cent	No.	Per Cent	Cumulative Per Cent
20 db or better	29	25.9		17	29.3		46	27.0	
21-25 db	29	25.9	51.8	16	27.6	56.9	45	26.5	53.5
26-30 db	30	26.8	78.6	10	17.2	74.1	40	23.6	77.1
31-35 db	11	9.8	88.4	5	8.6	82.7	16	9.4	86.5
36-40 db	4	3.6	92.0	4	6.9	89.6	8	4.7	91.2
41 or worse	9	8.0		6	10.4		15	8.8	
	112	100.0		58	100.0		170	100.0	

TABLE 3

STAPES MOBILIZATIONS

Hearing Level (db)	Group I Nov. 1954 to Dec. 1956			Group II Jan. 1957 to Dec. 1958		
	No.	Per Cent	Cumulative Per Cent	No.	Per Cent	Cumulative Per Cent
20 db or better	19	16.1		47	24.2	
21-25	7	5.9	22.0	18	9.3	33.5
26-30	7	5.9	27.9	23	11.8	45.3
31-35	9	7.6	35.5	18	9.3	54.6
36-40	12	10.2	45.7	19	9.8	64.4
41 db or worse	64	54.3		69	35.6	
	118			194		

however, are the immediate postoperative results, hearing levels between 1 and 3 months postoperatively. When the course of the patients was followed over a period of years, it was found that the success rate was no better than about 20 per cent. The enthusiasm for the mobilization procedure was, in fact, ill founded. It would appear probable that mobilization through a focus of disease would in all probability heal rapidly and again become fixed, and this indeed occurred in most cases. The interesting fact remains that some 20% of cases still have mobility of the stapes as shown by excellent hearing at the end of 3 to 5 years.

Mobilization of the Stapes

As time went on the next step in the evolution of surgery for deafness was a return to Kessel's original suggestion. Portmann[9] in Bordeaux and Shea[10] in Memphis both advocated the removal of the stapes from the oval window and the insertion of tissue to close the oval window. Shea used a vein graft and fixed a polyethylene prosthesis to the incus to replace the stapes. Portmann used mucous membrane and other tissues and reinserted the stapes or part of it onto the mucosal graft. In his operation he left the head of the stapes attached to the incus and to the stapedius tendon, and either replaced the whole bone or replaced the crura onto whatever tissue he had interposed in the oval window. The results were consistently better with this replacement surgery, but at first there was an expressed fear of opening the vestibule widely. In view of this, House[11] and Schuknecht[12] shattered the footplate without removing it. House then covered the shattered footplate with Gelfoam and put a polyethylene strut from the incus to make contact with the shattered footplate. Schuknecht used stainless steel wire for his prosthesis, looping it onto the end of the long process of the incus and having a little twist of wire which sat down on the shattered footplate. The results from shattering, however, were usually inferior to those from complete removal. In our own series immediate results, that is 1 to 3 months after operation, are indicated in table 4.

It is obvious that the results from complete removal of the footplate, or as Shea described it, "fenestration of the oval window," are superior to those of any other method. Fifty per cent of patients are restored to normal hearing, "10 decibel or better level for speech," and 86% to a "30 decibel level or better."

Various technics have been used for replacement of the stapes. Many surgeons attach to the incus stainless steel wire to which has been tied either a vein or a plug of fat to fill the oval window. Others use vein graft as advocated by Shea with a polyethylene prosthesis to the incus. Others use Gelfoam in place of a vein graft. It would seem immaterial which method is used, as the reported results are approximately the same in all series. These results, however, are immediate and we know nothing so far of long-term results.

It should be remembered, however, that in all series a small percentage of "dead" ears have been reported following surgery. In our own series of 6 failures 3 were unchanged by the operation, one has a "dead" ear and in 2 the hearing, though still present, is worse than before operation.

The indications for stapes surgery differ from those for fenestration of the horizontal canal. First, the operation from the patient's standpoint is relatively minor. If it fails the canal is not altered and a hearing aid can be worn. Further there is no morbidity following the operation. It therefore becomes possible to

TABLE 4

	Footplate Shattered			*Footplate Removed*		
Level	*No.*	*Per Cent*	*Cumulative Per Cent*	*No.*	*Per Cent*	*Cumulative Per Cent*
10 db or better	24	25.0		36	50.8	
11-20 db	17	17.7	42.7	17	24.0	74.8
21-25 db	10	10.4	53.1	5	7.0	81.8
26-30 db	12	12.5	65.6	3	4.2	86.0
31-35 db	8	8.3	73.9			
36-40 db	4	4.2	78.1	1	1.4	87.4
over 40 db	4	4.2	82.3	3	4.2	91.6
Failed	17	17.7		6	8.4	
	96	100.0		71	100.0	

TABLE 5

A. McC. *Date*		*500*	*1K*	*2K*	*3K*	*4K*	*6K*	*8K*	*H. L. Speech*	*Discrimination*
4/27/59 Preop.	AC	↓	↓	85	85	90	85	↓	0	0%-120
	BC	40	55	55	50	45	45			
RT										
7/18/60 Postop.	AC	70	70	70	65	75			67	64%-120
	BC									
4/27/59 Preop.	AC	85	95	80	70	100	90	80	88	56%-120
	BC	30	45	50	45	60				
LT										
7/18/60 Postop.	AC	50	50	50	50	60	60	80	52	64%-115
	BC	30	40	50	50	60				

operate upon persons with a mixed deafness if their ability to wear a hearing aid can be improved by the operation. Two of our "poor results" illustrate this point. A. McC. (Table 5) has been rehabilitated to the point where she can wear a hearing aid in both ears and this was impossible before the operation; G. P. (Table 6) is now hearing well with the treated ear and needs only a little amplification with a hearing aid, whereas she needed much amplification prior to operation.

We think there is one limitation to this operation, namely in the size of the external auditory canal. The operation becomes most difficult through a very narrow canal, and in some cases we have advised fenestration of the horizontal canal because of this limitation.

To summarize, then, surgery for deafness has made almost a complete circle. At first the avulsion of the stapes was advocated but led to serious results from infection. Next, fenestration of the horizontal canal was advocated and finally was perfected when Lempert described his technic. Then, mobilization of the stapes was attempted but with little success, and finally removal of the stapes has now become popular again and can be done because of improvements in technic, in instrumentation, in magnification and in the prevention of infection by the antibiotics. The results for removal of the stapes and replacement by a prosthesis are excellent immediately following the operation. Time alone will tell what the final outcome will be and whether we will again revert to the more certain operation of fenestration.

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TABLE 6

G. P. *Date*		*500*	*1K*	*2K*	*3K*	*4K*	*6K*	*8K*	*H. L. Speech*	*Discrimination*
4/21/60 Preop.	AC	65	70	95	↓ →	↓	↓	↓	82	48%-120
	BC	20	35	50	60	↓	↓	↓		
RT										
9/26/60 Postop.	AC	40	45	65	90	90	↓	↓	44	64%-110
	BC	15	30	40	50	65	↓	↓		
4/21/60	AC	55	55	75	100	↓	↓	↓	64	64%-120
	BC	10	25	45	55	65				
LT										
	AC									
	BC									

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Discussion (Abstract)

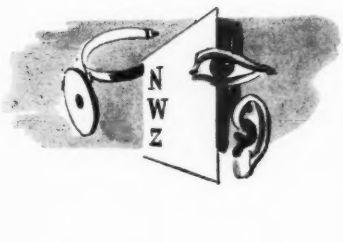
Dr. Joseph W. West, St. Louis, Mo. I am privileged to discuss Dr. Walsh's paper. His critical analysis of the results of the operations he has done for deafness reveals both his demand for detailed and accurate preoperative and postoperative evaluation and his enviable record of surgical accomplishment.

Dr. Walsh has described the rather strict requirements for the fenestration operation and has touched upon the differing indications for stapes surgery. Fortunately, the original enthusiasm for the stapes mobilization procedure has prompted the development of the various technics for the removal and replacement of the stapes, thereby permitting these different indications to remain effective. In addition to improving the ability of a patient with mixed deafness to use a hearing aid, the stapes procedures are being used for hearing losses of only 25 or 30 decibels and for instances of unilateral deafness.

These added indications have greatly increased the number of candidates for surgery for otosclerosis. These are not the only factors, however, in the growing number of patients undergoing such operations. The small morbidity, as compared with the fenestration operation, has encouraged both patient and surgeon alike. The possibility of improving the hearing to a level better than the theoretical limit of 20 to 25 decibels permitted by the fenestration operation has also given encouragement. We must give due credit to publicity concerning stapes surgery, both in the press and on television. I am also pleased to comment that more and more hearing aid dealers are recognizing clients with an air-bone gap and are referring them to the otologist for consultation.

This increasing opportunity for surgery for otosclerosis has prompted many more of us to begin this work than had ever considered doing fenestrations. We have been encouraged and helped by the instruction most willingly given by those who are outstanding in this work, by their publications, and by the workshops they have organized. We are indebted also to the development and availability of the operating microscope and the special instruments necessary for this surgery. Some senior residents in otolaryngology are now being trained in stapes surgery, and perhaps in the future every well-trained otolaryngologist will have been prepared for doing such operations.

These facts, however, should in no way diminish the responsibility which this opportunity requires. Those of us assuming this responsibility must see that we have the proper training or supervision, that we have the proper equipment, and that we study and follow our patients thoroughly, both before and after operation. Morbidity has been minimized. We are obligated, though, to advise our patients of their chances for complications, even of a "dead" ear, as well as their chances for improvement of hearing. We should quote them the figures of our own experiences, not the figures published by those with great natural ability and extensive experience. We are obligated to our specialty not to hide our poor results, but to add to a joint effort to find and to correct our mistakes. As the years come and go, we may help find the true role that this operation will play in the field of deafness.



Erythroblastosis Fetalis from the Obstetrician's Viewpoint*

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IT HAS INDEED BEEN A PROBLEM for your Chairman to select a topic for presentation fitting the honor you have bestowed on him. Lacking the gray hair—and even to some extent, the balding head—usually accompanying this office, it seems presumptious for me to stand before this Section and present "words of wisdom" to you at whose feet I have sat and shall continue to sit.

But, it being my duty to present a treatise worthy of this Section, I thought on obstetric subjects and decided that it would be well to review the present knowledge of erythroblastosis of the newborn and the problem of the iso-immunized mother from the obstetrician's viewpoint. This is a field which we share with our pediatric confreres and with our friends, the plasmologists.

It was also my desire to do an obstetric study from the Southern Baptist Hospital—a distant, and infinitely more sophisticated cousin of the Charity Hospital, from which most of our New Orleans contributions have sprung for the past century. One of the areas in which we believe we excel at Baptist is in our blood bank and immunohematology laboratory.

Organized by a pioneer in the field, Dr. Julius W. Davenport, under the direction of our Chief of Pathology, Dr. Hugh Lawson, the esteemed President of the Southern Medical Association, this blood bank has served an outstanding and useful service in intricate immunologic studies of specimens sent from a large area of the South.

It has occurred to me also that there is still much misunderstanding about the Rh problem, frequently resulting in mother and doctor alike becoming unnecessarily tense. At other times, perhaps, oversight and insufficient attention have resulted in the lack of study or prognostication in the case of an iso-immunized mother.

Perhaps to over-simplify for a moment, let us review some basic knowledge of the Rh factor. There are a number of different substances in the blood of certain humans which may act as antigens when introduced into other human beings, thereby creating antibodies. These antibodies will, if subsequently exposed to the same antigen, set up reaction to combat it. The antigen substances with which we are concerned here are those of the Rh series. General understanding of the intricacies of the Rh factor was at first hampered by the problem of nomenclature. Now we recognize three factors which go under the generic name Rh: Rh_0, rh′ and rh″. Rh_0 is so far and above all the most frequent cause of Rh allergies that a person designated as simply "Rh positive" implies the presence of the Rh_0 factor. Therefore, the term Rh has two meanings—one, to mean the entire series of Rh_0, rh′ and rh″, or its other and more practical meaning, the presence or absence of Rh_0.

Now let us see for a moment where the often misunderstood Hr factor fits into the picture. Since there are three major Rh factors —Rh_0, rh′ and rh″—there are three major correlating alternatives to take their place, if they are absent—Hr_0, hr′ and hr″.

A look at the more familiar gene having to do with the color of the eyes, though not completely analogous, helps to clarify the picture. Color of the eye is determined by the presence or absence of the brown gene. If brown is present in both genes, Br/Br results in brown eyes. If it is present in one location, one has Br/__with the other factor filled with the recessive blue, or Br/bl and the person still has brown eyes. Or, if the person were "brown negative" the two genetic locations of eye color would be filled by bl/bl, with no brown factor present. Similarly in Rh—one

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has Rh/Rh with both locations filled by the factor. If one is missing, however, (as in Br/bl) the other location has to be filled. Thus, the Hr gives this Rh positive individual an Rh/Hr pattern. If no Rh exists in this person he is said to be Rh negative, and therefore both locations are filled by Hr/Hr. The vast majority (about 92%) of antibody responses are due to Rh_0; the majority of the remaining responses to this series of antigens is due to hr′. Clearly it can be seen that if a person is Rh positive, he may or may not be Hr positive, depending on whether one Rh/Hr or both Rh/Rh fill his genetic pattern. It is also clear that if he is Rh negative, he must be Hr positive, since the genetic locations have to be filled.

To further complicate the nomenclature and understanding, in any place where designations Rh_0 or Hr_0 are used, D and d may be substituted. Similarly rh′ and hr′ are synonymous with C and c and rh″ and hr″ are also called E and e.

Time has brought about the discovery of still other factors in the blood besides the Rh family and A and B blood group factors. The Kell, the Duffy, the Kidd, the Lutheran and so forth, named principally for the people in whom they were first discovered, are also antigenic factors. The introduction of any of these factors into any person in whom they do not naturally occur is accomplished only by blood transfusion or by pregnancy. It is postulated that during pregnancy or delivery bits of fetal blood with factors inherited from the father are liberated into the maternal blood stream. Antibodies are built up which remain permanently in the mother's serum, waiting for subsequent inoculation to go into action. This action in the obstetric patient is the sending of the antibodies back through the placenta to combat the fetal blood, resulting in the well-known entity, erythroblastosis fetalis (EBF).

Erythroblastosis fetalis, or hemolytic disease of the newborn, varies greatly in degree and type. It is often divided into the true erythroblastosis fetalis, icterus gravis, and hydropic types. Its danger in the unborn is from the presence of anemia, which may be sufficient to cause intra-uterine death. This probably results from the failure of the hemopoietic system to keep up with the abnormal destruction of red blood cells. After birth, jaundice and the abnormally high presence of bilirubin cripple and kill since the fetus, particularly the premature, is not able to eliminate the substance rapidly enough.

Formerly, close checks were made on the blood counts of these babies, whereas now the frequent use of the quick and easily done microbilirubin is our best laboratory aid in following them. Allowing the bilirubin level to become too high results in kernicterus with damage of the brain and death, or permanent disability such as cerebral palsy. Tests have been evolved to determine the presence or absence of these antibodies in the obstetric patient's serum. Pooled blood cells known to contain the offending antigen are mixed with the serum to be tested under various environmental conditions (suspended in saline, suspended in albumin, subjected to trypsin enzyme incubation) which bring out the quality and degree of antibodies developed by the maternity patient. Considered the most sensitive of these is the Coombs' test, an indirect test observing the effect of immune serum on cells which have been previously exposed to the mother's serum being tested.

Clinical Studies and Interpretation

The present series consists of all the patients delivered at the Southern Baptist Hospital, New Orleans, in a period of 5 years (July 1, 1955-June 30, 1960), who were found to have antibodies during their pregnancies, or whose babies showed evidence of erythroblastosis fetalis of the Rh-Hr type. (A study is in process of the babies with EBF of the A-B-O type.) The series represents 214 cases studied (Table 1).

The results of the study are broken down

TABLE 1

SOUTHERN BAPTIST HOSPITAL SERIES
MOTHERS WITH ANTIBODIES OR INFANTS WITH ERYTHROBLASTOSIS
July 1, 1955—June 30, 1960

Erythroblastosis—Stillborns	23
Erythroblastosis—Neonatal deaths	16
Erythroblastosis—Exchange tranfusion and living (including 3 sets of twins)	128
Erythroblastosis—mild—no transfusion	24
Total EBF	191
Normal infants whose mothers showed Rh sensitivity	26
Total infants	217

TABLE 2

MOTHERS SENSITIZED BY PREVIOUS TRANSFUSION

23	Stillborns	3	13%
16	Neonatal death	1	6%
125	Transfused	8	6%
24	Mild	0	0
26	No EBF	0	0

into the following categories for further examination—23 women who delivered stillborn infants; 16 instances of EBF who died after birth; 125 pregnancies resulting in 128 babies (3 sets of twins) who had Rh or Hr EBF, and who received exchange transfusions and survived; 24 infants who were diagnosed EBF but did not require transfusion and lived; and 26 babies who had no EBF, although the mother was shown to have positive antibodies during the course of her pregnancy. This represents a total of 191 cases of EBF with 152 survivals, or an 80% survival rate.

It has been said that patients who are sensitized originally by incompatible blood deliver babies with a more severe degree of erythroblastosis fetalis. This is borne out to some degree by our series (Table 2). The incidence of mothers sensitized by transfusion was high among the stillborn group and absent in the mildly involved erythroblastotic group. It is interesting to watch the gradual decrease in numbers of mothers sensitized by transfusion, as the population transfused before 1943 gradually outgrows the childbearing age.

As to the antigenic factor to which these mothers had developed specific antibodies, table 3 illustrates among those tested the usual preponderance of Rh_0 (D) followed by hr′ (c). None in the 5 cases with EBF due to hr′ (c) factor represented an extremely severe case. Only one of the infants had two transfusions; and all babies in this group were hr′ (c) positive and Coombs' positive.

TABLE 3

ANTIGENIC FACTORS TO WHICH SENSITIZED
(Where Antigenic Specificity Was Determined)

Stillborn	17 Rh_0 (D)			
Neonatal death	10 Rh_0	1 Rh_0′(D, C)		
Transfused	68 Rh_0		5 hr′(c)	1 Rh_0″(D, E)
Mild	4 Rh_0			
No EBF	9 Rh_0		2 hr′	

TABLE 4

SEX DISTRIBUTION OF ERYTHROBLASTOTIC INFANTS

	Male	*Female*
Stillborn	10	13
Neonatal death	9	7
Transfused	65	63
Mild	9	15
Total	93	98

There were no significant differences in the strength of antibody levels in women sensitive to various factors.

Some question has been raised as to the difference in sex distribution of the babies with EBF. From table 4 it can be seen that there is a mild predominance of girls.

It was observed at one point in our study that there seemed to be an unusual number of abortions in the past histories of cases with EBF. Therefore, although it has been thought that Rh sensitivity does not cause early abortion, this factor in their history was analyzed. From table 5 it can be determined that the abortion rate was approximately 20% in each category (a little higher in the case of neonatal death). Although this average does seem high, no correlation was found to an increased number of abortions depending on the severity of the mother's sensitization.

There did seem to be more significant correlation between EBF and the presence of congenital anomalies (Table 6). The analysis shows approximately 4% of major congenital

TABLE 5

RELATIONSHIP OF NUMBER OF ABORTIONS TO NUMBER OF INFANTS IN THE PREVIOUS HISTORIES

Stillborn	1	abortion to a parity of	5.2
Neonatal death	1	" " " " "	3.2
Transfused	1	" " " " "	4.9
Mild EBF	1	" " " " "	5.0
No EBF	1	" " " " "	5.2

TABLE 6

ANOMALIES

Stillborn	None
Neonatal death	3 severe, multiple, incompatible with life
Transfused	2 congenital heart
	1 bilateral hernia
	1 "honeycombed" skull
	1 mongolism
Mild	1 hydrocephalic
	1 hallus valgus
No EBF	1 bilateral clubfoot

TABLE 7

OUTCOME IN CURRENT SERIES CORRELATED WITH PAST OBSTETRIC HISTORY OF ERYTHROBLASTOSIS

Number	*Stillborn*	*Neonatal Death*	*Transfused*	*Mild*	*No EBF*
6 Inadequate records					
7 No previous infants					
114 No previous EBF	1 (7%)	7	75 (82%)	19	12 (11%)
46 Previous EBF (none died)	6 (15%)	1	31 (76%)	4	4 (9%)
41 One or more previous infants died with EBF	15 (51%)	6	13 (32%)	0	7 (17%)
1 child	45%				
2 children	72%				
More than 2	100%				

abnormalities (excluding the milder anomalies) in the erythroblastotic group. This is in contrast to the generally accepted approximately 1% incidence of significant congenital malformation.

It is usually conceded that the past history of Rh negative mothers is one of the best means of prognosticating the outcome of subsequent pregnancies. Careful attention was paid to past histories in our series (Table 7).

As the history of past Rh involvement increases, the chances of the current pregnancy causing difficulty increases. Judging from our series, a woman who is shown to develop antibodies but who has no history of previous Rh problem, has a 93% chance of having a successful outcome (a fact often encouraging to a mother who gets her first result of positive antibodies). If, going further, she has a baby with erythroblastosis fetalis which is successfully treated, the chance of the next pregnancy having a happy outcome is 85 per cent. If she loses one, however, her chances for the next successful outcome falls to 49 per cent. With the progress of pediatric care these figures may be deceptive, for as we give better care to infants, a lost baby means a much stronger antigenic stimulation; whereas, formerly a lost baby may have been due to failure in adequately caring for and exchanging the blood of the baby at birth.

Jacobs[1] in his recent article questions the validity of preterm deliveries. His series fails to bear out a significant lessened incidence of erythroblastosis in infants delivered early over those of 40 weeks. He invites other series studied in the same way. Our data has been organized according to this timing for the sake of comparison; here, too, we see *no* lessened incidence in mortality among infants born before term. As is seen in table 8, the mortality of the premature baby is naturally high.

As to the fetal outcome following 37 weeks of gestation (Table 9), Jacobs divided these into the 37-38 week group, the 38-39 week group, and those at 40 weeks and more. In the first of these categories, 37-38 weeks, I found an 87.5% survival; in the 38-39 week group an 82.5% survival; and in the 40 week group an 89% survival, clearly no decrease of survival as full term is approached. When combined with Jacobs' series this gives a survival percentage in the 37-38 week group of 72%; in the middle group, 38-39 weeks, 81%; and in the full term, 40 weeks and up,

TABLE 8

FETAL OUTCOME OF ERYTHROBLASTOTIC INFANTS
(With Regard to Length of Gestation)

Duration of Pregnancy (Weeks)	*Total Delivered*	*Stillborn*	*Neonatal Death*	*Survived*	*Per Cent Survived*
26-32	10	5	4	1	10.0%
32-36	22	7	1	14	63.7%
37 & up	159	11	11	137	86.2%
Total	191	23	16	152	79.4%

TABLE 9

FETAL OUTCOME AFTER 37 WEEKS

	Total Cases	*Stillborn*	*Neonatal Death*	*Survived*	*Gestation (Weeks)*
Our series	40	4	1	35 (87.5%)	
Jacobs' series	50	7	13	30 (60.0%)	37-38 weeks
Combined series	90	11	14	65 (72.2%)	
Our series	57	6	4	47 (82.5%)	
Jacobs' series	32	2	5	25 (78.0%)	38-39 weeks
Combined series	89	8	9	72 (81.0%)	
Our series	63	1	6	56 (89.0%)	
Jacobs' series	28	6	1	21 (75.0%)	40 weeks and up
Combined series	91	7	7	77 (84.6%)	

84.6 per cent. With these figures before us, one may further question the advisability of delivery before term. However, statistics of this type are easily misinterpreted, and one has the thought, in reviewing the records of some of the full term stillborns where fetal movement disappeared after the due date, that had delivery before term been done, there would have been a better chance for survival. However, on the other hand, these might well have been added to the cases of early neonatal death.

An examination of the records of the 23 stillborn infants shows that 15 of the mothers had previously lost babies from the disease. Six of these patients had had previous babies treated for this condition who lived, and 2 had had no previous trouble. The majority of the stillborn infants were macerated, of the hydropic type and markedly premature. Only 5 records of this group show potentially salvagable babies in the light of our present treatment. The others were hydropic or died macerated in utero at a very early age. These 5 reached mature weight and were delivered from 38 to 40 weeks. However, as stated above, we cannot statistically confirm the value of early delivery. One case, though by no means conclusive, illustrates this point. Mrs. A. P. M., gravida 6, para 4, has 4 living children; the last two babies required exchange transfusions. Antibodies remained constant during the next pregnancy and she was repeatedly examined during the latter weeks having in mind the possibility of the induction of labor, but the cervix remained firm and closed. At thirty-nine and a half weeks she spontaneously went into labor and delivered a nonmacerated, 8 pound erythroblastotic stillborn infant, whose heart tones had been normal two days previously. It was thought an early delivery might have saved this baby, and it might have; however, 2 years later, antibodies remaining constant, labor was successfully induced and she was delivered of a 6 pound, 12 ounce baby at thirty-seven and a half weeks. The baby's appearance was normal at birth, but the cord blood showed a hematocrit of 21, hemoglobin 6.5 Gm. (a very unusual finding in our series), a bilirubin of 7 mg. and a strongly positive Coombs' test. Exchange transfusion was begun within an hour, but the condition had progressed so rapidly that the infant died during the procedure. It is rather likely that the previous stillborn child might have had a similar outcome, had labor been induced before term and the infant been born alive.

In examining the neonatal deaths it was found that of the 16 who died, 5 were delivered premature before 33 weeks of pregnancy, and 11 at 37-40 weeks. None of the prematures was transfused, 4 out of the 5 died within 2 hours (the other had multiple congenital anomalies). Nine of the remaining 11 had exchange transfusions—4 of whom died during the transfusion. Of these, it was not my impression that the exchange transfusion caused death so much as that these infants were impossibly and irreparably sick and that the transfusion occurred at the time of their rapidly increasing toxicity.

In the present study there were 128 babies, including 3 sets of twins, who were transfused and who lived. Table 10 shows the number of transfusions given. Four died during transfusion, but since it is believed that transfusion was more coincidental with death than the cause of it (though it may have been a precipitating factor), it is concluded that exchange transfusion in the hands

of the present-day team is a highly safe procedure.

In our series of 26 cases with antibodies, but without EBF, 19 babies were Rh negative. One did not have EBF, because the mother's sensitivity was to the hr′ factor and the baby was hr′ negative. This leaves 6 women with positive antibodies (some very mildly positive) whose babies would be expected to be erythroblastotic but who were not. Two of these even had a past history of EBF. These 6 represent false positive tests. This is the irregular problem which makes such a study as this interesting.

Coincident with this investigation there has been studied at Baptist Hospital a series of cases of idiopathic hyperbilirubinemia in which the infants have not been found to have erythroblastosis of either the Rh or A-B-O or any other type. It is interesting to note that in 3 of these cases, with past histories of erythroblastotic babies and currently showing antibodies specific for the anti-Rh_0 factor, there were idiopathic levels of hyperbilirubinemia varying from 11 to 22 mg. per 100 ml. These babies were all Rh negative and therefore were not erythroblastotic. They are included in the series because of the mothers' positive antibodies from previous babies. There is one additional nonerythroblastotic Rh positive, Coombs' negative baby from an Rh negative mother, with only a one plus trypsin (one of the group of 6 false positive antibodies) who showed idiopathic hyperbilirubinemia to a level of 17.6 mg. These 4 out of 26 cases in which there were positive maternal antibodies and without EBF (largely because the babies were Rh negative) lead us to suspect that there is a correlation between the Rh sensitivity and the idiopathic hyperbilirubinemia. Recent works by Kanter and collaborators[2] associate this with the albumin binding factor which carries the unconjugated bilirubin through its conjugation by the liver. The presence of antibodies (even without EBF) acting similarly to sulfonamides, caffeine, and aspirin, in some way prevents conjugation, leaving the toxic bilirubin resulting in jaundice.

TABLE 10

REPLACEMENT TRANSFUSIONS

	Number of Babies	*Number of Transfusions*
1 replacement transfusion	91	91
2 " "	23	46
3 " "	14	42
Total transfusions		179
Transfusions given to babies who died		9
Total		188
Died during transfusion 4	Mortality rate	2.1%

TABLE 11

SALINE AGGLUTINATIONS

	Negative	*1-2+*	*3-4+*
Stillborn	17	5	
Neonatal death	5	8	
Transfused	65	32	14
Mild	11	3	
No disease	21	4	1

A correlation was undertaken between the presence of various antibodies in the mothers and the outcome in the babies. The tests for saline agglutinations showed that among the 22 stillborns whose mothers had antibody determinations, 17 were negative and 5 were positive to one plus. Other results of the saline agglutinations are seen in table 11. Clearly, according to these findings, as one would expect, the saline agglutination test taken alone is of little prognostic importance in the potentially sensitized mother. These mothers have largely become hypersensitized and the agglutinins have been replaced by the blocking antibody.

Tests for blocking albumin antibodies in the mothers destined to have stillborns were positive in all 22 tested (Table 12). Among the neonatal deaths, 2 showed negative blocking as well as saline agglutination shortly before delivery. Both of these women had positive trypsin and indirect Coombs' tests and, incidentally, both had babies who had congenital anomalies incompatible with life. The large number of negative results in the transfused group illustrates that the blocking antibody test leaves much to be desired in dependability as to the prognostication in potentially sensitized mothers.

TABLE 12

ALBUMIN BLOCKING ANTIBODIES

	Negative	*1-2+*	*3-4+*
Stillborn	0	5	17
Neonatal death	2	6	5
Transfused	22	45	44
Mild	6	8	
No disease	9	11	6

TABLE 13

TRYPSIN ANTIBODIES

	Negative	*1-2+*	*3-4+*
Stillborn		4	18
Neonatal death		5	8
Transfused		41	73
Mild	1	11	1
No disease	1	16	9

In the trypsin test, on the other hand, there was only one mild case of EBF showing a false negative reaction in the mother (Table 13). This baby showed a one plus Coombs' test, but was so mildly ill one questions the diagnosis of erythroblastosis. The mother showed a questionably positive indirect Coombs' test with all other antibodies negative. The only additional case with a negative trypsin test was in a case of false positive blocking with no evidence of disease. My study shows the trypsin incubation test for antibodies in the mother's serum to be a highly sensitive and useful test for prognostication of erythroblastosis fetalis.

In reviewing these cases, one is impressed with the significance of the forewarning and forecasting of the trypsin test. For example, one woman, gravida 2, para 1, and with no history of EBF or sensitivity, was tested prior to the beginning of her second pregnancy and not found to have antibodies of any type. At 33 weeks she was found to have doubtful positive agglutinations and blocking, and a 2 plus trypsin test and a negative indirect Coombs' test. At 36 weeks, agglutinations and blockings reaction and indirect Coombs were all found to be negative, whereas the trypsin test remained positive. The baby was delivered at 40 weeks, found to have a 3 plus direct Coombs' test and was transfused for erythroblastosis fetalis.

Another woman was tested at 9 and 24 weeks gestation, and was found to be negative to saline agglutinations, blocking and indirect Coombs reactions. She had a 3 plus trypsin test on both occasions. At 34 weeks the blocking and saline agglutinations had changed to 3 plus and she was delivered at 37 weeks of an erythroblastotic baby which required two transfusions. This indicated the early prewarning value of the trypsin reaction. There are several other cases which further illustrate this point of the sensitivity of the trypsin test. Early in this study the presence of a mildly positive trypsin reaction and absence of other antibodies was considered insignificant and discounted. As some of these patients were followed through subsequent pregnancies, however, it appeared that the presence of a positive trypsin reaction may forewarn of significant antibodies in later pregnancies, even if it is falsely positive in the current one. Continued study over a long period of time will deny or confirm this. The finding of a positive indirect Coombs' test added to a positive trypsin reaction, is relatively certain to result in an erythroblastotic baby.

Discussion

In our obstetric service we recommend an Rh_0 determination on each maternity patient (Table 14). Those who are Rh negative, or multiparas who are Rh positive with any question of a related problem in their history, have an Rh determination on the husband, the patient being sent to the blood bank for saline agglutination, albumin blocking, and trypsin incubated antibody studies.

If these tests are negative, no further studies are made until the tests are repeated one month from term.

If they are equivocal (such as negative blocking reaction and trypsin test doubtful or positive), or if there is an unusual history suggestive of more complicated Rh problems, an indirect Coombs' test is done.

If the Coombs' test is positive or if there are significant antibodies in the albumin and trypsin tests, the specimen is tested to a panel of known cells to determine the specificity of the antibody.

Our method of expressing the presence of antibodies is by a quantitative estimate (one to four plus) of the avidity—or vigor—of the antibody. We reserve the more expensive

TABLE 14

ROUTINE OF RH STUDIES

All Obstetrical Patients—Rh_0 Determination	
If Rh negative or Rh positive with questionable history	Husband—Rh determination Wife—agglutinations, blocking, and trypsin antibody studies
(a) If antibodies negative	Repeat at one month from term
(b) If antibodies equivocal or unusual past history	Indirect Coombs Repeat studies at 36 weeks
(c) If original antibody positive or if Coombs is positive in (b)	Test with a panel of known cells for antibody specificity. Repeat studies at 36 weeks

and time-consuming quantitative titer (degree it can be diluted and still show a positive reaction) for the exceptional case.

Mothers who show any degree of antibody response should be delivered in surroundings where prompt and adequate treatment can be given to their babies. The value of early delivery is questionable; however, with a favorable cervix we induce labor between 38 and 40 weeks. Cord blood is drawn by venipuncture from one of the distended veins of the fetal surface of the placenta. Fetal Rh type, bilirubin, complete blood count and direct Coombs' reaction are determined immediately. As an extra precaution cord blood is drawn for Rh, type, and Coombs' tests on *all* Rh negative mothers (even those without antibodies and on those with Rh_0 negative husbands). Babies with laboratory evidence of EBF are watched closely and treated early and vigorously by exchange transfusion. The bilirubin test is an important guide in following these cases.

Nursery personnel are urged to be on the alert for jaundice in all babies whether of Rh negative mothers or not. Although we do not do routine antibody studies on patients who are hr′ negative, unless there is a history of past hr′ sensitivity, this factor and others in the Rh-Hr series can cause EBF. Also, it is the clinical picture in the baby which usually alerts the diagnosis of A-B-O hemolytic disease as well as "idiopathic hyperbilirubinemia."

Some of the pitfalls and errors which a study of this series has shown are as follows:

1. Failure to do an Rh test in mothers, especially in primigravida.

2. Error in testing the father (calling an Rh positive man negative).

3. Failure to test for antibodies in early and latter pregnancy for comparison.

4. Failure to deliver the infant in surroundings with adequate facilities when antibodies have been shown to be present.

5. Unnecessary concern by physician and Rh negative patient when antibodies are consistently negative.

6. Failure to check the mother's blood after delivery for all sources of antibody activity when the baby develops an unsuspected jaundice. These mothers should be re-tested as to type, Rh, Coombs, antibody determination of Rh series, A-B series, and rarer antigens.

There is as yet no proven way of preventing iso-immunization. I have on two occasions done Aldridge's reversible sterilization of virtually hopelessly sensitized mothers with homozygous husbands. We have not had occasion to release these tubal fimbriae from their broad ligament pockets because we have not yet found the answer to our problem. Bioflavonoid, though not claimed to be a panacea, may reduce the immunizing response by protecting the small vascularity of the placenta and fetal tissue against bilirubin. Further studies will be necessary to determine this.

We put in one final plea for the best protection of these babies at the time of delivery. They are sick babies, and it is easy for the additional problems of anoxia, atelectasis, birth trauma, or prematurity to sway the outcome unfavorably. All consideration should be given to preventing these factors by handling these deliveries without trauma and without excessive sedation, thereby turning the babies over to the pediatrician in as good condition as possible.

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Management of Recurrent Intestinal Obstruction Due to Adhesions*

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Recurrent adhesions are a foregone conclusion subsequent to operations for adhesions and obstruction. To obviate these complications the author has used internal splinting for over a decade to obtain "controlled adhesions."

RECURRENT INTESTINAL OBSTRUCTION due to adhesions remains a problem. Methods to prevent the reformation of released adhesions generally have been unsatisfactory.[1] Simple lysis of adhesions alone may fail because during the healing process adhesions may recur and, in many instances, may cause acute angulation of the bowel and recurrent obstruction. The unfortunate patient with recurrent intestinal obstruction often exhibits multiple abdominal operative scars, and frequently is addicted to narcotics. Usually, he is a poor surgical risk, and poses a challenge to surgical therapy.

In 1955 I described an operative procedure for preventing recurrent obstruction of the small bowel due to adhesions.[2] The technic utilized the principle of splinting the denuded small bowel on a long intestinal tube after the release of adhesions. By using the semirigid tube, the position of the intestine would be maintained in large coils with an assured patent lumen; and, as the adhesions reformed, which they inevitably would do, the new adhesions would be controlled adhesions. Sharp kinks with the attendant danger of subsequent obstruction would be prevented.

A long-term follow-up usually is necessary to determine the effectiveness of an operative procedure. Eleven years have now elapsed since the denuded bowel was splinted successfully on a long tube to correct recurrent intestinal obstruction in the first patient so treated. Because the procedure has been of some general interest, it is timely that our subsequent experience with the procedure be reviewed. Particular reference will be made to variations in surgical technic.

Our results with the first 16 patients reported in 1955 are presented in table 1. As followed up to 11 years, a recent survey of the original group revealed that none of the patients has required additional surgical treatment for intestinal obstruction (Table 1).

Experience in 20 additional patients has been very satisfactory in that obstruction has not recurred during the usual period of postoperative observation nor has a single death occurred.

This favorable clinical experience has been confirmed by certain experimental evidence. In a study to compare the effectiveness of the tube-splinting technic with the Noble plication procedure,[3] Heydinger, Taylor, and Roettig[4] produced extensive intestinal adhesions in dogs. At subsequent operations the tube-splinting procedure was performed to prevent recurrent obstruction in one group of dogs for comparison with the Noble plication procedure which was done in another group. Postoperative roentgen studies showed "the accordion configuration and the almost 180 degree angle which is produced by the Noble plication procedure. Partial breakdown following a Noble plication is shown....." A follow-up gastrointestinal series on the group treated by the tube-splinting procedure re-

TABLE 1

THE SPLINTING PROCEDURE
(Results in 16 Patients)

Satisfactory Results	13 Patients
13 patients followed—1 year or more	
9 patients followed—3 years or more	
4 patients followed—5 years or more	
Unsatisfactory Results	2 Patients
1 death after operation—embolus (?)	
1 failure—patient developed subsequent obstruction	
Not Followed beyond uncomplicated postoperative convalescence	1 Patient

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vealed "the intestine to be in good position. Comparison demonstrates well the more normal anatomical and physiologic configuration produced by the tube procedure as compared with the Noble procedure." These authors concluded that, "The striking difference in the two procedures is the time element. The average time needed to plicate the intestinal loops by the Noble procedure was seventy-three minutes. In contrast, a twenty-three minute average time was needed to complete the tube procedure." By using the tube-splinting technic, good clinical results also were obtained in 10 patients.

Technic of Tube-Splinting Procedure in Various Types and Degrees of Intestinal Obstruction Due to Adhesions

General measures. (1) Preoperatively, it is desirable to decompress the distended gut by passing, if possible, a long intestinal tube past the ligament of Treitz.

(2) If oral feedings are tolerated, the bacterial flora of the bowel is reduced by antibiotic therapy.

(3) Following the surgical procedure, the tube must remain as a splint for 10 to 12 days to permit formation of sufficiently strong adhesions to maintain the intestines in large loops and to assure a patent lumen.

(4) The total length of the intestinal tube should be utilized in the splinting to prevent telescoping of the bowel on the tube. Harris[5] has shown that the entire small bowel may be threaded on only 3 feet of tube, but this is undesirable in the splinting procedure.

Tube-splinting of total small bowel. After all adhesions are released, the long intestinal tube is threaded manually into the terminal ileum by manipulation or by enterotomy and the use of a vein stripper. The patient is more comfortable if the upper end of the tube is brought out through a gastrostomy rather than by maintaining the nasal route for the necessary 10 to 12 days. Upper gastrointestinal distention is relieved by gastric suction through small perforations cut in the tube within the stomach. The tube is placed to, but not through, the ileocecal valve. After peristalsis has returned, oral feedings are well tolerated. Generous amounts of mineral oil for lubrication and removal of the mercury bag permit easier withdrawal of the tube in 10 to 12 days.

If a long intestinal tube has *not* been passed into the small bowel preoperatively, a jejunostomy serves admirably for the entrance of the long tube above the upper adhesive area.

Tube-splinting of segments of small bowel. Short segments of denuded bowel can be splinted if desired. The terminal ileum is usually the site involved. A rather stiff plastic tube can be inserted readily through a cecostomy and threaded through the bowel in a proximal direction with anticipation of good results.

Acute small bowel obstruction due to extensive adhesions. Great care should be exercised in splinting the acutely obstructed intestine because of the danger of contamination and excessive manipulation of the bowel in these seriously ill patients.[6] First, the bowel is aseptically decompressed at operation by a special trocar.[7] Irrigations of saline are used to remove thick intestinal contents, and monoxychlorosene (Clorpactin WCS 90) (0.4%) is instilled into the gut to reduce the bacterial count.[8] Complete lysis of adhesions and tube-splinting then may be accomplished safely as described previously.

Comment

The tube-splinting procedure has merit because:

(1) It can be accomplished readily and relatively quickly in the poor risk patient with recurrent intestinal obstruction due to adhesions.[4]

(2) It is adaptable to various types of intestinal obstruction, such as those associated with fistula.

(3) It may be combined with other valuable adjuncts as segmental resection and/or by-pass procedures.

(4) The procedure gives assurance against obstructing kinks during an early postoperative period; and, when combined with gastric suction, prevents troublesome postoperative distention.

(5) It is of prophylactic value in avoiding obstruction after certain procedures where the protective peritoneal surfaces must be sacrificed as in pelvic exenteration.

(6) Tube-splinting is especially valuable after repair of large ventral hernias with many intestinal adhesions.

Conclusions

Experimental and clinical evidence now has accumulated sufficiently to suggest that splint-

ing of the denuded small bowel on a long intestinal tube for 10 to 12 days is a valuable procedure for preventing recurrent obstruction of the small bowel due to adhesions. Patients have been treated with good results up to 11 years postoperatively.

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Discussion (Abstract)

Dr. Eugene M. Bricker, St. Louis, Mo. It is a pleasure to be asked to discuss Dr. White's paper since I believe he has made a very significant contribution. I remember very distinctly when Dr. White first spoke on this subject before the Southern Surgical Association. For some months we had been using intestinal intubation at the operating table in a somewhat similar manner and for a similar purpose. Naturally I was disappointed that I could no longer claim the idea as new and original. I agree completely with Dr. White regarding the effectiveness of this technic in the prevention of recurrent intestinal obstruction. We have had occasion to use it rather extensively as a prophylactic measure in patients in whom a pelvic exenteration has been done. It is my distinct impression at this time that by use of a long intestinal tube we have appreciably cut down the incidence of postoperative intestinal obstruction in these patients. Whether or not this is actually so will have to await further study of our material. Nevertheless, I am convinced enough that I use it on all patients who have extensive pelvic surgery and, like Dr. White, I have had occasion to use it in other complicated abdominal situations. The complications incident to the intestinal intubation itself have been minimal and are greatly outweighed by the benefits derived from the wonderful control of the patient it affords. Time does not allow me to go into details of how we use the long tube. It is one of the fundamental surgical principles that one does not adopt another man's idea and procedure without improving upon it. We have some slight technical differences with Dr. White which may or may not be improvements. One difference I might mention is that we buy a standard type of red rubber tubing in 50 foot lengths which stands autoclaving very well and which is put out in appropriate lengths as needed. Holes are cut in the tubing by the surgeon as desired. The tubing is much less expensive than the standard long intestinal tubing which I believe Dr. White is using. Perhaps such an economy measure is not necessary in Texas.

Again I wish to congratulate Dr. White on the development of what I consider to be an extremely useful technical maneuver that can greatly reduce the hazards of some complicated abdominal and pelvic operations.

Better use medicines at the outset than at the last moment.—Publilius Syrus (Circa 42 B.C.) Translation by Darius Lyman.

Primary Myoglobinuria and Exercise-Induced Secondary Myoglobinuria: A

Report of 7 Cases Seen at an Army Basic Training Center

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No doubt this condition is more frequent than recognized. Though in its subclinical forms it may be of no significance, when it rises above the clinical horizon it should be recognized for what it is, for analysis, reassurance and for advice as to prophylaxis.

THE PHENOMENON OF MYOGLOBINURIA is not as rare as previously thought. In the past year and a half, 12 articles[1-11] have appeared, and 9 new cases of primary myoglobinuria were presented,[1-9] increasing the total number in the literature to approximately fifty. Furthermore, 21 cases of secondary myoglobinuria were also reported, 2 the result of arterial embolism with ischemic myopathy,[10] and 19 following muscle injury from excessive exercise.[11]

It is the purpose of this paper to stress the relative frequency of myoglobinuria by reporting another case of the primary form, and 6 more patients with secondary myoglobinuria due to exercise injury of muscles, all treated at this hospital during an 18 month period from July 1958 to December 1959. A brief review of the present knowledge of the condition and a new classification of the various forms are also presented.

Myoglobinuria is often a serious condition, usually related to exercise and characterized by muscular dysfunction and the passage of red-brown urine.[12-14] A total of 14 deaths have been reported in primary myoglobinuria and in myoglobinuria associated with identifiable myopathies;[1,9] there also have been several deaths from the secondary form of myoglobinuria.[14] Since treatment at best is supportive, attempted prevention of the condition assumes great importance, especially in the basic training centers of our Armed Forces where unaccustomed exercise is the rule.

Methods and Material

The cases reported include 4 patients treated by me and 2 seen by other physicians during 1959. One other case was found by a review of the hospital records of the previous 6 months. The decision to present this series was made after all the patients had been discharged from the hospital. One of them, Case 2, still at the Fort, was recalled and exercised. He had a mild recurrence and therefore represents the only case observed from before the onset of an episode.

Because of the limited laboratory facilities at this hospital, on several occasions urine was sent to other institutions for either spectrophotometric (Third U. S. Army Medical Laboratory, Fort McPherson, Ga.) or electrophoretic (Veterans Administration Hospital, Columbia, S. C.) analyses to positively identify the urinary pigment. Unfortunately positive identification was not made.

Case Reports

Primary Myoglobinuria

Case 1. K. L., a 23 year old white male recruit, entered the hospital on the 5th day of active duty. The day after arrival at the Fort, bilateral calf tenderness and stiffness had appeared, with thigh tenderness the following day. On the 3rd day the patient felt weak, feverish and chilly. All symptoms continued and on the 5th day red-brown urine was voided and the patient was therefore admitted to the hospital. The patient had performed unaccustomed exercise in the form of marching and some "double-timing," but this is considered to represent only mild to moderate

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exertion; he had not yet begun basic training. A similar episode had not occurred previously, and the family history and review of systems were noncontributory.

The patient was a well-developed young man. The *physical examination* was normal except for mild tenderness of the calves, and edema, heat and marked tenderness of the thighs. Temperature was 104° F. orally, P. 140, and B.P. 140/98 mm.Hg.

Laboratory findings. Initial WBC. count was 12,300 with a normal differential count; follow-up counts were normal. Hematocrit was 47% and the plasma was of normal color. The sedimentation rate was 15 mm. per hour (Wintrobe). Initially, the urine was brown and contained 4+ albumin, with 5 to 6 WBC., rare RBC., and 4 to 5 coarse granular and occasional hyaline casts per hpf. Thereafter, casts were no longer observed; RBC. were not seen after the 2nd hospital day; albuminuria and the brown color lasted through the 5th day, but the urine remained benzidine-positive (after centrifugation) through the 6th day. A screening test for porphyria was negative. Urine urobilinogen was positive 1:20. A urine concentration test showed 1.015 as the highest specific gravity; a specific gravity of 1.022 was achieved several days later. The following serum constituents were normal: BUN., bilirubin, albumin, cholesterol, sodium, potassium, calcium, and phosphorous. S.T.S. showed no reaction.

The patient was treated supportively with bed rest, warm soaks and forced fluids. In spite of an average daily fluid intake of 3,500 cc., begun at admission, there was mild transient oliguria: urinary output was 650 cc. the 1st day, 1,000 cc. the following day, and then rose subsequently to more than 3,000 cc. daily. Severe edema and tenderness of the thighs and generalized muscular soreness lasted until the 3rd hospital day. Blood pressure returned to normal on the 3rd day. Thereafter, the patient rapidly improved. The urine was normal after the 6th day; all muscular complaints were absent after 2 weeks. During the 3rd week he was permitted full activity about the hospital, and when no recurrence was observed, he was returned to full duty without restriction.

He tolerated basic training and subsequent duty over a 6 months period without return of his complaints. At the time of discharge from the Army, routine physical examination and urinalysis were normal.

Comment. This patient presents a clinical picture entirely compatible with the published descriptions of primary myoglobinuria.[12-14] The onset was acute and was initiated by moderate exertion. Generalized muscular pain and weakness, chills, fever, and the passage of red-brown urine, which was benzidine-positive in the presence of a normal-colored serum, are all characteristic of the syndrome. The transient renal damage, indicated by oliguria; red blood cells and casts, is a common occurrence.[3]

This case supports the findings of others[9,13,14] that response to exercise may be variable. It suggests that factors in addition to exercise are perhaps necessary to initiate the release of myoglobin, for subsequently this patient was able to tolerate the severe exertion of basic training without suffering a recurrence.

Exercise Myositis with Secondary Myoglobinuria

Case 2. W. B., a 24 year old white male recruit, entered the hospital on the 23rd day of active duty. Three days before the patient had taken a physical training (P.T.) test. He had been a "physical culture" enthusiast in civilian life and was accustomed to vigorous exercising. Because he thought he might win a "three day pass" promised to the man with the highest score, he forced himself to a greater performance than ever before. One exercise in particular, "squat-jumps,"* caused marked exertion of the legs; he performed 106. The day after the test he had marked pain and tenderness of the thighs, which became progressively worse the following day. In spite of this he continued training. That evening he voided red-brown urine; the following morning the color of the urine was lighter. He reported to the dispensary and was admitted to the hospital. He denied previous episodes and did not recall the condition in any member of his family.

The *physical examination* was normal with the exception of brawny, hot and markedly tender thighs. T. was 98.6° F. orally, P. 72, and B.P. 112/72 mm.Hg.

Laboratory studies. Routine blood counts were normal, and the plasma was of normal color. Examination of the urine revealed a brown color, a positive reaction with benzidine, 1+ albuminuria, 12 to 15 WBC. and 3 to 6 RBC. per hpf. Spectrophotometric analysis categorized the pigment only as a "hemochromogen," which could not be identified as myoglobin. Follow-up urinalyses were normal. S.T.S. was nonreactive.

Other than painful thighs, the patient felt well. He was treated supportively by bed rest, hot packs and forced fluids. Within 3 days he was able to walk without pain, and was discharged to duty without restrictions on the 6th hospital day. He then completed basic training and advanced infantry training without a return of symptoms.

Second hospitalization: Five months later the patient was requested to repeat the P.T. test in an attempt to reproduce the syndrome. He complied, and although he did not achieve as high a score as previously, he was able to do 97 squat-jumps. Bilateral quadriceps muscle pain began the following day and grew progressively more intense. On the 3rd day after the test he was again hospitalized.

Urinalyses were performed immediately before and after exercise and were normal (Table 1). Urinalyses were obtained each morning for 5 more days. Al-

*Squat-jumps are performed as follows: a deep knee-bend with one foot in front of the other, a quick jump to upright posture with the position of the feet reversed during the jump, and then down into another deep knee-bend.

TABLE 1

THE RELATIONSHIP OF EXERCISE AND MUSCLE TENDERNESS TO URINE FINDINGS DURING THE SECOND EPISODE OF MYOGLOBINURIA, CASE 2

Date	Degree of Muscle Tenderness	Urine Findings: Albumin	Benzidine Reaction (Supernatent)	WBC.*	RBC.*	Casts*
Feb. 10, 1960						
3 p.m. (before exercise)	0	0	0	Rare	0	0
6 p.m. (after exercise)	0	0	0	2-3	0	0
Feb. 11						
6 a.m.	++	0	0	1-2	0	0
Feb. 12						
6 a.m.	++++	Tr.	Tr.	8-10	2-4	0
Feb. 13						
6 a.m.	++++	+	Tr.	0	0-1	1 hyaline 1 RBC. 1 granular
Feb. 14						
6 a.m.	++	Tr.	0	1-2	0	0
Feb. 15						
6 a.m.	+	0	0	2-3	0	0

*Per high-powered field.

though frankly brown urine did not appear, the urine reacted positively with benzidine for 2 days, albumin was found on 3 days, and red cells and casts appeared transiently. Paper electrophoretic identification of myoglobin by the method of Whisnant and associates[3] was unsuccessful. Routine blood counts and the color of the plasma were normal.

While hospitalized the patient was treated with bed rest and hot packs. Edema and tenderness were thought not to be as severe as before, and he was again discharged to duty after 6 days. There are no evidences of residual muscle weakness or atrophy.

Comment. Although the patient was carefully observed, the urinary pigment could be classified only as a hemochromogen and absolute identification was not obtained. Spectrophotometric evidence is compatible with, rather than diagnostic of, myoglobinuria since the absorption spectra of myoglobin and hemoglobin are very similar.[3, 5] It is thought that paper electrophoresis was unsuccessful because the protein was not present in sufficient concentration in the urine: the benzidine reaction was only positive to a trace, compared to the strongly positive benzidine reaction in the urine of the patient of Whisnant and associates.[3]

Cases 3-7. Five other cases are so similar in detail to Case 2, that only a combined summary will be presented. The patients were white male recruits, 17 to 23 years of age. All took the P.T. test given at the end of the second week of basic training. All performed prodigious numbers of squat-jumps, spurred on by the promise of a weekend pass. Soreness of the quadriceps muscles appeared within 12 to 24 hours after the test, and brown urine was voided 12 to 48 hours after the pain appeared. None had had previous episodes and all had negative family histories. The initial urinalyses showed 2+ to 4+ albuminuria, brown color, and a positive reaction with benzidine. A few RBC. and casts were occasionally seen. Red-colored plasma was not found. Urinary findings returned to normal within 1 to 3 days. An average of 5 days hospitalization was required. Residual muscle weakness or atrophy was not seen. All returned to duty and completed their training without difficulty.

Comment. These cases, as well as Case 2, represent a form of myositis with secondary myoglobinuria described in detail only recently.[11] They demonstrate that severe repetitive exertion can traumatize muscle, resulting in the release of large quantities of myoglobin. Undoubtedly other cases have occurred at this installation but did not come to medical attention. (That subclinical myoglobinuria may develop is shown clearly in Case 2; during the patient's second episode, myoglobin was detected only by daily testing of the urine with benzidine, rather than by urine color.)

Discussion

It has been demonstrated that the loss of minute amounts of myoglobin in the urine is a normal phenomenon following strenuous exertion.[15] It is not surprising, therefore, that the release of larger amounts of the protein with clinically recognizable myoglobinuria is a relatively more frequent occurrence than had been thought. The large number of reports appearing recently attest to this. Wider dissemination of knowledge about myoglobinuria will result in an increasing recognition of the syndrome. Therefore, a brief review of the physiology, pathology, diagnosis, classification, and treatment of the condition is

offered. If a more complete discussion is desired, a number of excellent reviews are available.[3,9,12-14]

Physiology. Myoglobin, a protoporphyrin-globin complex, is a red protein which acts as an oxygen reservoir in muscle.[12] The molecule is essentially one fourth of the hemoglobin molecule, but differs slightly in the globin fraction.[9] The concentration varies directly with physical fitness as well as the daily work requirement of each muscle group, for example, occurring in especially high quantities in those muscles concerned with walking. When released into the blood it remains unbound by plasma proteins, and its low molecular weight (17,000) permits rapid filtration by the glomeruli, so a concentration higher than 15 to 17 mg. per 100 cc. of blood is never attained. This is too low to impart the red color of myoglobin to plasma.[5,10] Freshly voided urine containing the pigment is red-brown, but an even darker brown color rapidly appears as metmyoglobin forms.[5]

Pathology. In the majority of those studied by biopsy there have been variable degrees of muscle degeneration,[9,13,14] occurring either on an idiopathic basis, or secondary to a metabolic defect,[7] or some physical[11] or chemical insult.[12] With muscle injury myoglobin is released into the blood stream and is filtered into the urine. That the mechanism of release of myoglobin is not simply a function of cellular dissolution is shown by the lack of myoglobin in other diseases of muscle degeneration.[9]

Myoglobinuria usually results in some degree of renal damage, for uremia has appeared in one third of the reported cases and albumin, cells and formed elements were noted in most of the others.[3,11,16] The most common cause of death from primary myoglobinuria is uremia.[9] All of the cases in this report showed evidence of transient, mild to moderate renal damage without residual effect. The lesion responsible is acute tubular necrosis;[3,11] the exact pathogenesis of this lesion (i.e., a nephrotoxic effect of myoglobin versus ischemia) has not been elucidated experimentally as yet.

Diagnosis. Myoglobinuria should be suspected clinically whenever a chief complaint of muscular pain or weakness is followed by the excretion of red-brown urine which is benzidine-positive and contains insignificant numbers of red blood cells.[3] Porphyria is ruled out easily by the appropriate screening test. However, the condition must be differentiated primarily from the various hemoglobinurias,[16] especially "march hemoglobinuria" in which red-brown urine appears 3 to 4 hours after strenuous exercise, but is *not* accompanied by tender or swollen muscles.[16]

In myoglobinuria the plasma color is normal.[5,10] This differs from hemoglobinuria in which the plasma is always red; liberated hemoglobin is immediately bound to haptoglobin, resulting in a molecule too large (310,000) to be filtered by the glomeruli. Hemoglobinuria occurs only after the hemoglobin-binding capacity of haptoglobin is exceeded. Thus a concentration high enough (70 to 150 mg./100 cc.) to impart red color to plasma is reached before excretion by the kidneys begins.[5,10]

The addition of 2.8 Gm. of ammonium sulfate to 5 cc. of fresh urine will precipitate only hemoglobin, a simple test for differentiating myoglobinuria from hemoglobinuria. The test must be performed promptly before the formation of metmyoglobin which is also precipitated.[5]

There are several laboratory methods employed to identify myoglobin. Two of the tests must be considered as suggestive, not diagnostic: ultra-centrifugal analysis may yield sedimentation constants compatible with myoglobin, but there are other urinary proteins with similar constants;[3] as noted previously, spectrophotometric analysis also does not give definitive results, for the curves of both myoglobin and hemoglobin are quite similar.[3,5] On the other hand, both the electrophoretic method of Whisnant and his coworkers,[3] and the serologic test of Ono[15] provide absolute identification.

Clinical Classification. Several authors have developed classifications of the types of myoglobinuria, but the use of differing terminology has caused confusion.[1,2,9,12-14,16] The terms suggested by Whisnant and coauthors[3] appear to be the most appropriate, and are employed in the following proposed classification which includes all known forms of human myoglobinuria:

1. Primary myoglobinuria (paroxysmal).
   a. Recurrent with subsequent exercise.[7,16]
   b. Apparently nonrecurrent or inconsistently recurrent with further exertion.[13,14]
   c. Not related to exercise.[3]
   d. Rapidly fatal form.[1]
2. Myoglobinuria in primary muscle disease.[17]
3. Secondary myoglobinuria.
   a. Crush injury.[12,13]
   b. High voltage accidents.[12,13]
   c. Exercise myositis.[12,18-20]
   d. Haff disease.[12,13]
   e. Occlusion of artery supplying large muscle mass.[10]
   f. Carbon monoxide poisoning.[13]

Primary Myoglobinuria. Cases included under this heading are, by definition, those thought to be caused by intrinsic metabolic defects or deficiencies of muscle. Schmid and Mahler[7] recently were first to demonstrate such a defect. Their patient had muscle necrosis with recurrent myoglobinuria following exercise, and was shown to lack phosphorylase activity in the muscle and was unable to convert muscle glycogen to glucose-1-phosphate. However, 2 other patients with the same metabolic error did not show myoglobinuria, indicating that the entire mechanism of myoglobin release is not explained by this study. Muscle anoxia due to defective oxygen utilization caused by an abnormal myoglobin also has been proposed as a cause of myoglobin release,[9] but comparative studies of the physical and chemical properties of myoglobin from patients and normal persons have yielded no difference.[3,9] It is probable that a variety of metabolic defects related to oxygen and energy utilization will be found to explain the various clinical patterns observed.

Paroxysmal myoglobinuria is related to exercise in over half the reported cases.[9,13,14,16] Until the exact etiology is known it seems reasonable, as proposed by Korein and coauthors,[9] to employ this relationship to exertion in classifying patients. In some males and in almost all female patients, the attacks have not been preceded by exercise[3] and even have occurred during sleep.[13] Among those patients whose first attack followed exercise, subsequent reactions to exertion are variable.[13,14] Some patients have had severe recurrences with renal "shutdown" following effort.[16] On the other hand some patients have only a single attack: our patient (Case 1) was able to resume basic training and complete 6 months of army life without further difficulty. The 6 month follow-up is not prolonged enough to state that he will not have a recurrence; in most patients followed for sufficiently long periods, exacerbations have been observed.[6] The rapidly fatal form of the disease refers to patients who succumbed to a first overwhelming attack, dying either of uremia[3,9] or from the complications of progressive paralysis.[1]

Myoglobinuria in Primary Muscle Diseases. Myoglobinuria has been observed in patients with identifiable primary muscle disease.[17] The cases reported are either related to, or are actually forms of muscular dystrophy or dermatomyositis. This special form of myoglobinuria is given an intermediate classification, as it does not conform to the definitions of either the primary or secondary conditions.

Secondary Myoglobinuria. This term implies recognizable preliminary damage to the musculature. The subgroups listed in the classification have all been well described in the literature for several years. However, only recently has "exercise myositis" been clearly defined as a separate entity in an excellent report by Howenstine,[11] who presented 19 cases in Marine recruits. He showed that repetitive calisthenics (squat-jumps) resulted in muscle injury; occasionally hemoglobin as well as myoglobin was excreted. There have been only three other reports of similar cases. de Langen's subject, a prisoner in a concentration camp, had myoglobinuria, identified spectroscopically, following repetitive punitive exercise (knee-bends); the thighs were tender and swollen.[18] Pearson, Adams and Denny-Brown[19] identified myoglobinuria in a patient with damage of the pretibial muscles following repeated skipping. Five university students, reported by Stahl,[20] passed dark urine following repeated punitive or competitive exercises (knee-bends or push-ups); the muscle groups primarily stressed by the exertion (shoulders or thighs) were swollen and painful.

Our cases also illustrate that repetitive

strenuous exercise of specific muscle groups may create enough damage to release myoglobin in gross amounts. This appears to be an extention of the finding by Ono[15] that traces of myoglobin are normally present in the urine after strenuous effort. Fifty-two of 56 athletes studied by him had positive tests for myoglobin, and 2 actually voided red urine.

This form of myoglobinuria probably has been confused occasionally with primary myoglobinuria. For example, in 1959 in a case reported as primary myoglobinuria, the description of punitive exercise with resultant local muscular trauma strongly suggests a diagnosis of "exercise myositis."[2] Since primary myoglobinuria in the majority of patients also appears after exercise, the differentiation of the two entities may be difficult but usually can be made from the history and the clinical picture. First, there is a difference in the type of exertion. In Case 1 (primary myoglobinuria) only mild to moderate generalized exercise was performed and an attack ensued; several muscle groups were involved. In Cases 2-7 (secondary myoglobinuria), a *repetitive, localized* exercise, in the form of squat-jumps, resulted directly in trauma to the quadriceps muscles. This large muscle mass has a high concentration of myoglobin[12] and gross myoglobinuria occurred.

The clinical appearance of the patients usually presents a second difference; in primary myoglobinuria most often there is a constitutional reaction, characterized by chills, fever, malaise, and *generalized* muscular weakness and tenderness. The illness is prolonged. In contrast, our patients, those of Stahl,[20] and 14 "benign" patients reported by Howenstine[11] exhibited only *localized* muscular trauma and, other than the local discomfort, felt entirely well; all but 3 of these 25 patients were afebrile. All were fully recovered in 5 to 6 days. Strenuous exertion was resumed without recurrence in Howenstine's and in our patients, except for one (Case 2) who was able to create a mild recurrence by voluntarily exercising excessively.

Not all cases of "exercise myositis" are benign.[19] Muscle atrophy can occur, as in the patient reported by Pearson and collaborators. Five of the patients described by Howenstine[11] had prolonged recoveries due to marked renal damage, and one of them (Case 15) also had a constitutional reaction suggesting either an unrecognized intercurrent infection or a severe "toxic" response to the release of massive amounts of myoglobin.

Treatment

There is no specific treatment. General measures as heat and rest are indicated. Forcing fluids and alkalinization of the urine have been suggested to try to prevent renal tubular damage.[5,12] If the urine pH can be maintained above 6, oxy-myoglobin forms, a more soluble compound which is less likely to precipitate in the tubules.[12] However, in the face of progressive renal shutdown this form of therapy will be dangerous.

Prevention of myoglobinuria secondary to exercise myositis is of importance in the armed services where great stress necessarily is placed upon physical prowess. The avoidance of the use of exaggerated repetitive exercises, and the employment of adequate physical training to develop general fitness prior to competitive P.T. testing will help to prevent this disease. Ono[15] has found that trace-myoglobinuria disappears as the intensity of exercise is increased and fitness improves. At this army post, for the past 6 months, squat-jumps have been eliminated from all P.T. tests performed early in training, and since then no further patients with myoglobinuria have been seen.

It has been suggested that patients who suffer myoglobinuria following exertion be cautioned against *all* undue exercise.[1-3,6,14] Since subsequent response to exercise is often variable, exercise tolerance should be investigated carefully to avoid limiting the patient unnecessarily.[9,13,14] In primary myoglobinuria exertion may precipitate a severe exacerbation.[16] Therefore, in these patients gradually increased exercise should be employed to discover the patient's limits. In secondary myoglobinuria due to exercise myositis, there will be few recurrences upon careful physical conditioning and with a warning to the patient to repeat the offending exercises only in small but progressive increments.

Summary

Seven cases of myoglobinuria are presented together with a brief review of current knowledge of the condition. A classification of

forms of the syndrome is offered. It is suggested that secondary myoglobinuria due to local muscle trauma from repetitive exercise is probably common, but until recently has been overlooked. The title "exercise myositis with secondary myoglobinuria" is proposed for this type of myoglobinuria. It was present in 6 of our patients; the other had primary myoglobinuria. Since treatment of the condition is only supportive, the importance of prevention of exercise myositis by proper physical conditioning is stressed.

Acknowledgment

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Granuloma Annulare*

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I CHOSE THE SUBJECT Granuloma Annulare as a symbol of the thoughts I hope to develop. Browning said: "On the earth the broken arcs; in the heaven a perfect round" (Abt Vogler). In day-to-day living the broken arcs confront us—often in very very small fragments. Our aim is to complete the ring.

For at least twenty years I have been fascinated by the well-established and confidently recognized disease granuloma annulare. But is it an established entity, and is it identified with confidence?

In 1894, Radcliffe-Crocker[1] presented a case as lupus erythematosus resembling lichen planus, but shortly afterwards he recognized his error and described it as an independent clinical entity under the name of granuloma annulare. Graham Little[2] pointed out that, "Largely no doubt owing to Dr. Radcliffe-Crocker's selection of this term (granuloma annulare), it will eventually win in the competition for supremacy" in nosology. Little's prediction has proven to be correct.

There is much criticism of the term because the condition commences as a nodule and not as an annular lesion and the histologic finding is not that of a "granuloma." As far as is known it is not of an infectious origin. The name is established, whether appropriate or not, and probably is here to stay.

Colcott Fox[3] first drew attention to the disturbance now recognized as granuloma annulare when he presented for diagnosis an 11 year old female patient with an unusual, ringed eruption on the fingers. He was unable to make a satisfactory diagnosis, commented that this patient did not show rheumatic nodules, and wondered if she did not have erythema elevatum diutinum. From the recorded description it seems safe to conclude almost certainly that this patient had granuloma annulare. However, absolute proof that the diagnosis was correct was not supplied. No biopsy was done.

Four years after the report of Fox, Galloway[4] collected 13 similar cases from the literature and added a case report of his own. Galloway noted that 6 of the group reported by others occurred in men past middle age who were "tainted with gout or with gouty dispositions." He concluded, "It appears therefore that there are certain chronic inflammatory conditions of the skin which produce lesions resembling in many points those of lichen planus, and caused by poisonous substances in the circulation, the nature of which is not yet defined. These lesions vary among each other in the amount of congestion present, their duration, and the clinical appearance they present. Some of them show remarkably circinate or even annular mode of advance. They do not suppurate. They agree in all probability in their chief clinical characters and in the histological changes they produce. It is possible that gout and rheumatism are the underlying causes which produce some of the examples of this cutaneous malady. The cases produced by these diseases appear to be more marked by congestion and edema, and to be less regular in distribution than are other cases in which the influence of gout or rheumatism is more remote. Other causes, the exact nature of which is not understood, are capable of producing a group of eruptions very similar to those associated with gout and rheumatism but less erythematous and more regular in their distribution and form."

In the 61 years since Galloway made this statement, has much been added to the understanding of granuloma annulare, to being able to make the diagnosis, to settling its etiology, to linking it with other ailments and to predicting its clinical course? Also it is wondered whether much has been added to its therapy, to which point Galloway did not direct attention.

In 1908, Graham Little[2] published an exhaustive paper which summarized reports published by several observers who had employed a diversity of nomenclature such as Ringed eruption (Colcott Fox), Eruption Chronique Circinée de la Main (Dubreuilh), Lichen annularis (Galloway), Granuloma annulare

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(Radcliffe-Crocker), sarcoid tumors (Rasch), Neoplasie circinée et nodulaire (Brocq), Erythymato-sclerosis circinée du dos des mains (Audry) and Tumores benigni sarcoidei cutis (Galewski). Graham Little added to the group 6 cases which had not been reported previously. He felt that all these cases were related and he was convinced that it was possible to reconcile the differences indicated in the very diverse terminology adopted. One wonders if all of these cases collected by Little,—and this was pointed out by the author in his manuscript—had granuloma annulare, for histologic examination was not carried out on all.

For various reasons which seem valid, such as curiosity regarding cause, chronicity, benign course, suggestive histological simularity and no other acceptable etiology, efforts to connect granuloma annulare with tuberculosis were made. Among those first to propose such a relationship were Radcliffe-Crocker,[1] Little,[2] and particularly Chipman[5] who believed that if a thorough-going search for tuberculosis were instituted in every patient with granuloma annulare, a higher percentage having tuberculosis would be revealed.

Many investigators, Michael,[6(a)] E. Epstein,[6(b)] Prunty and Montgomery,[6(c)] S. Epstein,[6(d)] Bugarski,[6(e)] and Vissian,[6(f)] attempted to connect the disease with or disassociate it from tuberculosis. Several were of the opinion that there was some evidence in favor of a tuberculous etiology, but the majority thought such evidence did not exist and that the disease must be due to an unknown infectious agent—the same conclusions reached by Galloway[4] many years earlier. So, early in the study of this ailment, association with rheumatic and gouty disposition and with tuberculosis were proposed. It was recognized that other causes were capable of producing this disease.

More recently Grupper[7] classified granuloma annulare as a "collagenosis" and Gougerot[8] included it with his "allergides." Perhaps granuloma annulare, like many other morphologically and clinically typical entities, may be of different causes in different cases. To this day the precise cause or causes has not been established and certainly there is no convincing proof that the ailment is connected with or is a part of rheumatism, gout or tuberculosis. Its cause remains unknown.

For fifty to sixty years the clinical picture has been well established after the early descriptions of Radcliffe-Crocker,[1] Colcott Fox,[3] Dubreuilh,[2(a)] Galloway,[4] Rasch and Gregersen,[2(b)] Brocq,[2(c)] Audry,[2(d)] Galewski,[2(e)] Little[2] and others. Dermatologists regard this chronic inflammatory disease of the skin, characterized by deep seated whitish or pinkish flat-topped nodules which spread peripherally to circular and crescentic lesions, as being readily recognized. Little[4] effectively described the initial lesion, subsequent developments, clinical appearance, distribution (most common on the hands and next in order of frequency come the feet, ankle, neck, elbows, knees and the buttock), course of the eruption, subjective sensations (sudden appearance and only rare itching), incidence of season, age and sex.

During the years since the first histologic description many studies have been directed to the histologic findings, and a diversity of opinion regarding the significance and differentiating features observed in granuloma annulare have been described.

The early observers described the identifying histologic findings as little affection of the epidermis, perhaps slight thickening of the stratum corneum but no acanthosis and no thickening of the rete.

In the corium the sub-papillary zone is almost normal but the infiltration becomes more marked and more extensive deeper in the skin and the more superficial inflammation is a continuation of that which has taken place in the deeper zones. These findings were described by Graham Little:[2]

"The most significant changes amounting to tumor formation take place in the zone where the corium and hyperderm meet. Microscopic nodules are thus formed. The nodules often but not always show areas of degeneration with elastic and connective tissue fibers being absent. The cell masses, both when lying in clumps and surrounded by connective tissue and when interspersed in rows between the fibers, appear to be of the same type and to be composed chiefly of three kinds of cells: (1) A large mononuclear cell, staining vividly with nuclear dyes, larger than a leucocyte, but without the protoplasmic envelope of plasma cells, such protoplasm as is present being like a thin halo with the nucleus in the center. These are probably the largest constituent of the cell mass. (2) Numerous spindle-shaped, or oblong or pear shaped cells, not staining so deeply as the above, with an elongated nucleus, and in-

distinguishable from connective tissue corpuscles. (3) A few large faintly stained 'epitheloid cells,' interspersed in the cell mass."

Histologic findings have been recorded in many studies dealing with this subject, and additional knowledge has been added to that recorded by the early observers. In 1942, Prunty and Montgomery[6(c)] reviewed 31 cases with granuloma annulare observed during a 25 year period at the Mayo Clinic. They pointed out that varying degrees of degeneration of connective tissue were observed and that the elastic tissue was not proportionately involved. Changes in the vessels were minimal. They were able to demonstrate a substance giving a positive reaction to stains for mucin in all their cases. This finding was regarded as being significant in differentiating granuloma annulare from necrobiosis lipoidica diabeticorum, and Prunty and Montgomery concluded that on the basis of histological findings granuloma annulare could be separated from necrobiosis lipoidica diabeticorum, sarcoid and erythema elevatum diutinum.

However many disagree on this point. Ellis and Kirby-Smith[9] suggested that although the clinical and histologic picture is usually sufficient to allow differentiation, there was some evidence that the two syndromes (granuloma annulare and necrobiosis lipoidica) might be variants of the same disease. They noted striking simularity between necrobiosis lipoidica diabeticorum and granuloma annulare, and wondered if the microscopic variation might not depend on age of patient, location of lesion and a general or local alteration of the lipid metabolism. Ellis[10] reported a severe uncontrolled diabetic who had clinical and histologic features more suggestive of granuloma annulare than those of necrobiosis lipoidica diabeticorum.

Laymon and Fisher[11] stated that the epidermal changes in granuloma annulare and in necrobiosis lipoidica diabeticorum were usually unimportant unless there was ulceration which at times occurs in necrobiosis lipoidica. The most significant changes occur in the connective tissue where in granuloma annulare sharply marginated spheroid or ellipsoid areas of intense degeneration arranged in a radial or palisade fashion are usually formed. The infiltrate in both diseases is made up of varying proportions of fibroblasts, lymphocytes, histiocytes and epitheloid cells. Fibroblasts may be very prominent and internal proliferation and obliteration changes in the blood vessels are much more frequent and prominent in necrobiosis than in granuloma annulare. Deposits of lipids are almost always present in necrobiosis, but they may be present at times in granuloma annulare. They conclude that with the use of various methods of staining the two diseases can be differentiated histologically.

In a recent and very important study Wood and Beerman[12] used various current histological histochemical technics designed to demonstrate mucin, hemosiderin, lipid and glycogen deposits, PAS positive diastase resistant deposits in degenerated areas and PAS positive diastase resistant material involving the vessel walls and deposited in the vessel lumens. They conclude that a morphologically similar pattern may be found in all three conditions and that absolute differentiation by histologic examination is not possible. They did state that mucin was much more commonly associated with lesions of granuloma annulare.

So to this day the ability to separate granuloma annulare from necrobiosis lipoidica and perhaps at times sarcoid is not always certain.

The treatments of this disease have naturally been varied and numerous. The dermatologists who first described the disease applied salicylic acid ointment, usually 10% concentration, and at times ichthyol was added to the salicylic acid ointment. Tar lotion was used and Fowler's solution of arsenic was prescribed. Ointments of glycerin of subacetate of lead applied on lint were employed. Sequeira[2(f)] was probably the first to observe spontaneous resolution and Jadassohn[2(g)] made a similar observation. Little[2] and Adamson[2(h)] noted resolution of granuloma lesions after biopsy. To quote Little, "The course of the eruption is very varied. The longest duration noted in any case was seven years. Lesions untreated appear to be extremely indolent and to show little tendency to spontaneous cure, but when treated the most obstinate lesions seem to be dispersed by quite simple means such as maceration."

Many reported on the effectiveness of superficial radiation. C. J. White[13(a)] was one of the first to report benefit from x-ray treatment and shortly thereafter Hartzell,[13(b)] Chargin,[13(c)] Stillians[13(d)] and others reported on the effectiveness of superficial radiation. Ultra-soft rays

have been found helpful. Hansen[14] reported that electrolysis gave better results than x-ray, radium or arsenic. O'Farrell[15] reported spontaneous clearing in two patients after an attack of measles, while another patient did not clear after a high temperature from nasopharyngitis suggesting that fever alone does not produce the improvement. Welsh[16] found vitamin E combined with panthothenic acid deriatives effective when administered in large doses. Born[17] proposed treatment along the lines of rheumatologic therapy and suggested that there may be a connection between granuloma annulare and rheumatologic problems because both responded to the same type of therapy. Intradermal injection of hydrocortisone of prednisone, freezing with solid carbon dioxide applied to the lesion, incision and biopsy of the papules, injections of streptomycin and bismuth are other treatments which are effective.

In a recent article Mandel[18] reported on the effectiveness of chloroquin in a patient suffering disseminated granuloma annulare. This patient responded when chloroquin was administered, had a relapse after chloroquin was discontinued, and again responded when chloroquin was given again.

So in summary we are dealing with a disease which at times during the past 65 years has been recognized with considerable confidence. In fact, Ruben Nomland[19] stated that in his opinion about 50% of the patients with granuloma annulare do not have the typical microscopic features described in textbooks. Therefore which is more reliable: the clinical impression or the histologic confirmation? At times this disease has a very distinctive clinical picture—at times not so distinctive clinically. There is argument whether the histologic picture is distinctive and characteristic or whether various clinical entities are only variants of a common underlying pathologic process that can be initiated and produced by various causes. Of the many etiologies which have been proposed none have been proven the correct cause. Therapy has been many and varied and always entirely empirical. Spontaneous remissions occur and it is doubtful if any type of treatment is significantly effective. Therefore we are dealing with a clinical entity that has been recognized for a number of years. The cause is unknown, the histology is uncertain, the clinical course is unpredictable and questionably influenced by the various treatments.

Now, what is the lesson in this? What have we done as physicians and dermatologists to try to clarify the situation? Have most of us been content to sit still and follow along in the same pathways, or are we still interested in searching and exploring other possibilities leading to understanding its cause and perhaps connecting it with some systemic disorder.

To me this is the real challenge, and I would like to present to you this challenge—this ailment—granuloma annulare—as being symbolic of our problems in the field of dermatology. We must not be content with being able to recognize and to put a name on the disease and then sit back and feel that we have accomplished a great deal. This is something, but this is not enough. In this and many other diseases we are confronted with what these ailments manifested in the skin mean to the individual as a whole. And granuloma annulare is only a prime example, one of many that offers us a constant challenge. The same can be said of many other diseases which we diagnose daily from a clinical and histologic standpoint, but about the cause of which and the significance to the individual as a whole we actually know practically nothing.

Basic research absolutely essential though it is—is not enough either. So many skin diseases, problems presenting in the skin cannot be produced in laboratory animals. Furthermore, all of us who are dedicated to the search and understanding of truth are also physicians dedicated to service—service to our fellow beings who happen to be sick and seek our aid, our technics, our knowledge, and I hope, our wisdom. So, in the final analysis the clinical application is the final test—the test of useful truth.

It is true there are only patches of light in an area mainly dark; the unknown is vastly greater than the known, and the fringe regions are the abodes of the monsters laziness, indifference and lack of curiosity, but the fringes are also the abodes of fabulous knowledge and fabulous understanding if we push on. This can be done by using new technics in re-examination, but above all by careful clinical observations on the part of men with inquiring minds. We must move onward and I am sure we will.

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Post-Tonsillectomy Analgesia: A Double-Blind Study Comparing Pentobarbital, Codeine and a Placebo

THOMAS D. GRAFF, M.D., OTTO C. PHILLIPS, M.D., ALFRED T. NELSON, M.D., LEROY C. HARRIS, M.D., EDWARD T. FOX, M.D.,† and TODD M. FRAZIER, Sc.M.,‡
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There has been controversy concerning the effectiveness of these medicaments in the post-operative control of pain. With controlled studies the authors find codeine a most effective means of preventing postoperative excitement, delirium and agitation.

THE POSTOPERATIVE MANAGEMENT of the child who has undergone a tonsillectomy can be a difficult and harrowing task not only for the attending physician and nurse but also for the observing parents. Not infrequently, when such patients have received as preanesthetic medication a combination of a barbiturate and scopolamine, they respond to postoperative pain with a decorticate irrationality manifested by varying degrees of restlessness and combativeness. This can constitute a real threat to their physical well-being.

As a result of numerous studies on the analgesic properties of old as well as new drugs, an apparent dichotomy of opinion has developed among practicing physicians as to the more suitable pharmacologic approach to postoperative pain. Certain authorities[1,2] are of the opinion that small repeated doses of a short-acting barbiturate will provide adequate analgesia which, combined with its hypnotic action, offers ideal drug therapy in the large majority of patients with surgically induced pain. Others[3,4] hold to the attitude that the barbiturates are strictly hypnotic drugs, and that narcotic analgesics are the best pharmacologic answer to postoperative pain. Such lack of conformity of opinion is perhaps engendered by the widely divergent nature of the imposed surgical trauma and the frequent failure of the intensity of pain, as a symptom, to correlate with the severity of this trauma.[5]

The purpose of this investigation was to compare the short-acting barbiturate, pentobarbital, and the mild analgesic alkaloid, codeine, as to their relative effectiveness in controlling the restlessness and irrational state so frequently seen following tonsillectomy in children. The study benefited by being limited to a well-confined age group of patients who received identical preanesthetic drugs, and who underwent a specific surgical procedure.

Method

Included in this study were 60 children, with an age range from 2 to 10 years, on whom tonsillectomies were done under general anesthesia, and who, following recovery from anesthesia, were returned to a four-bed pediatric room for continued observation. The children were admitted to the hospital on the morning of the operation. Preanesthetic medication was given intramuscularly one hour preoperatively according to the following regimen:

Pentobarbital:	1.3 mg. per pound body weight
Scopolamine:	Under 3 years—0.1 mg. total
	3 to 6 years—0.2 mg.
	Over 6 years—0.3 mg.

Immediately prior to the induction of anesthesia, the effect of the preanesthetic medication was noted. The patients were judged as being cooperative, apprehensive or combative. Anesthesia was then induced with a cyclopropane-ether sequence by means of a to-and-fro, nonabsorption, bag and mask technic. Maintenance of anesthesia was carried out with an oxygen-ether insufflation through a Boyle-Davis Mouth Gag.* Note was made of

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cases in which difficulty was encountered in maintaining a clear airway, as well as of cases in which the surgical procedure was complicated by excessive blood loss. At completion of the operation a rubber catheter was passed to the stomach and any gaseous and liquid contents were removed by suction.

Upon arrival in the recovery room the patients were given an intramuscular injection of one of the three unknown "analgesic" agents, the dose of which was determined by the anesthesiologist on a volume per weight basis of 0.02 cc. per pound body weight. The three drugs included in the study were made up in the following concentrations:

1. Codeine phosphate 20 mg./cc.
2. Pentobarbital sodium 50 mg./cc.
3. Placebo

Each of the three agents had been prepared and placed in 5 indistinguishable 20 cc. vials giving a total of 15 vials. The appearance of the vials was similar in every way, except for the assigned code numbers. The order of administration of the drugs was at random according to a predetermined schedule. The identity of the drugs was unknown to the anesthesiologist, the nurse administering the drug, and to the attending nurses in the recovery room and the pediatric room.

The following postoperative data were recorded during a three hour observation period that had its beginning with the awaking time.

1. *Awaking time:* This was by definition judged to be that time elapsing from the end of the surgical procedure until the patient objected by gross movement to imposed respiratory obstruction (occluding the mouth and nostrils) within three attempts at inspiration.
2. *Degree of vomiting:* This was classified as follows:
   a. Absent.
   b. Transient retching or vomiting.
   c. Repeated retching or vomiting.
3. *Mental status of the patient after awakening:*
   a. Quiet, fully reactive to mild stimulation.
   b. Restless, complaining of discomfort, crying.
   c. Completely irrational, thrashing, combative.

These observations were made in the recovery room and in a four-bed pediatric room. Transfer of the patients from the recovery room to the pediatric room was made when the children reacted to verbal stimulation, such as the calling of their names. The average length of stay in the recovery room following the determination of the awaking time was 10 to 15 minutes. The remainder of the three hour observation period took place in the pediatric room.

TABLE 1

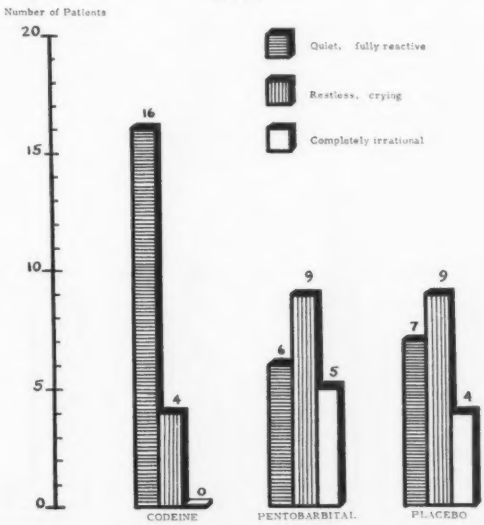
CLASSIFICATION OF CASES ACCORDING TO POSTOPERATIVE MEDICATION AND MENTAL STATUS

	Drug					
	Codeine		*Pentobarbital*		*Placebo*	
Mental Status	*No.*	*%*	*No.*	*%*	*No.*	*%*
Quiet, reactive	16	80	6	30	7	35
Restless, crying	4	20	9	45	9	45
Completely irrational	0	0	5	25	4	20
Total	20	100	20	100	20	100

Results

The reaction of the children while under the observation of the pediatric room nurse is shown in figure 1 and tabulated in table 1. The cases are classified according to the particular medication they received in the recovery room and the reaction of the children during this early phase of their postoperative course. The number of cases graded as quiet, restless or irrational were significantly different for the drugs tested ($p < 0.02$). Eighty per cent of the patients who received codeine were classified as quiet, whereas only 30 and 35% respectively for pentobarbital and placebo were in this state. None of the children who received codeine became irrational during this phase of the observation period. Pen-

FIG. 1



Observations in pediatric room. Classification of cases according to postoperative medication received and mental status observed.

tobarbital is seen to offer no advantage over the placebo in preventing a restless or an irrational postoperative course. During their short stay in the recovery room (approximately 10 to 15 minutes following the determination of the awaking time), the differences in the reactions of the three groups were less striking than those noted in the remainder of the three hour period and, though suggestive, are not statistically significant (Fig. 2).

In table 2 are listed certain factors which might rationally be considered as possible contributory or inciting factors in producing postoperative excitement and restlessness. The distribution of such factors as the presence of preoperative apprehension or excitement, problems in maintaining a satisfactory airway, and the excessive loss of blood during operation gives no indication that our results were weighted unduly in favor of any one medication.

Of importance in the evaluation of any analgesic drug is the nature and extent of undesirable side effects. None of the children, regardless of the analgesic received, showed any clinical signs of excessive depression of either respiratory or cardiovascular function. As noted above, the children classified as "quiet" were fully reactive to the mildest of stimulation, such as the raising or lowering of the side-rails or the calling of their names.

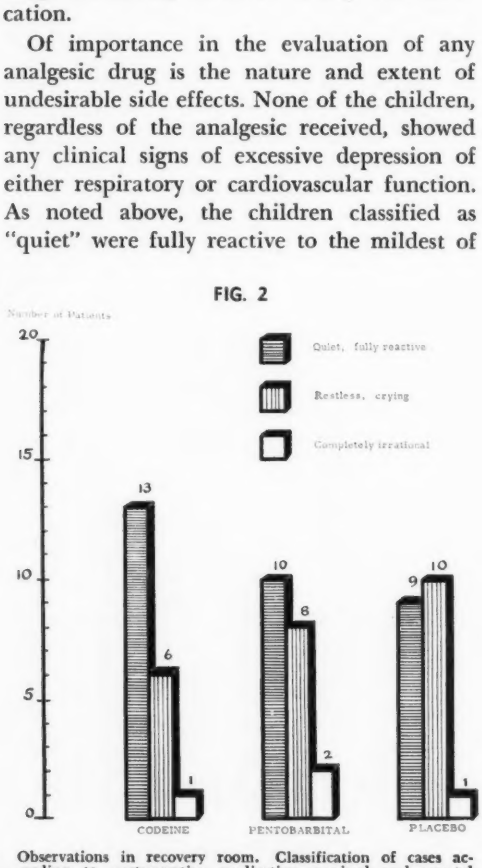
Nausea and vomiting were minimal problems in this series of patients. While in the recovery room, 10 of the children had transient retching during the awaking period. Of these, 4 had received the placebo, 4 codeine, while 2 had been given pentobarbital. During the observation period in the pediatric room, only 3 patients were described as having transient retching with minimal productive vomiting. All of these 3 had received the placebo as their "analgesic" agent.

TABLE 2

DISTRIBUTION OF FACTORS POSSIBLY CONTRIBUTING TO A POSTOPERATIVE RESTLESS OR IRRATIONAL STATE

Possible Influencing Factors:	*Postoperative Medication*		
	Codeine	*Pento-barbital*	*Placebo*
	Number of Cases		
Preanesthetic status:			
Apprehensive or combative	5	3	4
Undue airway problems	1	1	2
Unusual operative blood loss	3	2	1
Awaking time:			
Under 10 minutes	7	9	7
10-29 minutes	8	10	10
Over 30 minutes	5	1	3
Anesthesia time:			
Under 30 minutes	12	8	10
Over 30 minutes	8	12	10
Average age in years	4.9	4.8	5.4

FIG. 2



Observations in recovery room. Classification of cases according to postoperative medication received and mental status observed.

Discussion

Scopolamine is probably the most common of the anticholinergic drugs used today for pediatric preanesthetic medication. It has a powerful inhibitory effect on the secretory glands of the upper respiratory tract and affords a degree of depression of the central nervous system that effectively reduces excitement and anxiety. In addition, the partial or total amnesia resulting from therapeutic doses of scopolamine has obvious merit in the over-all management of the impressionable pediatric patient. In the presence of pain, however, the drug, rather than producing a state of tranquility, is prone to cause restlessness, delirium and agitation.

By referring to our control or placebo group, who received only normal saline postoperatively, it is apparent that 7 of the 20 children had little or no pain following full recovery from anesthesia (Fig. 1). These children were quiet, fully reactive and showed no signs of needing further medication. Such

a finding is not surprising in lieu of the experience of others. Thus, Keats[6] claims that pain does not invariably follow surgery, and supports that claim by citing that 21% of 104 patients who had undergone either a gastrectomy or colectomy received one or no dose of narcotic during the entire postoperative period. Papper and his group[7] found that pain was severe in only about one third of patients following operation. Nevertheless, 13 of the 20 children in our placebo group did manifest the presence of pain and 4 of these were totally irrational requiring constant physical restraint.

By contrast, of the 20 children who received codeine on admission to the recovery room, all but 4 were quiet although fully reactive. None in this group were irrational, nor in need of other than the routine post-tonsillectomy care and attention. The pentobarbital group, on the other hand, showed no difference in response to their postoperative experience than those in the placebo group. Five were agitated to the point of being totally irrational.

That a hypnotic drug alone, such as pentobarbital, is not the agent of choice in the management of the restless patient suffering pain was stressed by Leigh,[3] who advocated in its place an opiate. Hill, Belleville and Wikler[8] found that pentobarbital not only lacked any potent analgesic effect, but in addition failed to relieve experimentally induced anxiety. The now classic, but controversial, studies of Wolff, Hardy and Goodell[9] showed that the pain threshold in man could be elevated 60% by codeine, but to only a minimal degree by the barbiturates.

In any discussion of analgesia and surgically induced pain, consideration must be given to the extensive work of Beecher and his coworkers.[10,11] They developed in their clinical laboratory a practical method of evaluating the effectiveness of analgesic drugs in affording relief of postoperative pain. They pioneered technics of establishing effective controls to eliminate bias on the part of the investigators. Data was collected according to a preconceived plan that made possible sound and valid statistical analysis. From this group has come convincing data which demonstrated that pentobarbital produces analgesia with significantly greater frequency than a placebo. Thus, pentobarbital produced pain relief in 50% of their postoperative patients as compared to only 20% of patients receiving normal saline.

In showing no superior analgesic effect of pentobarbital over that of a normal saline placebo, our results are at variance with the data reported by Beecher. Possible factors responsible for this discrepancy might include our use of scopolamine preoperatively, as well as the restriction of our patient sampling to a pediatric age group. A large number of Beecher's subjects who benefited from the use of pentobarbital were judged to be more comfortable but not necessarily less aware of pain. Thus, a careful distinction was made between increased comfort and actual relief of pain. The children in our series, under the effect of the partial to complete decorticate action of scopolamine, very likely were unappreciative of such a fine distinction. That these patients benefit from the analgesic properties of an opiate was recognized by Slater and Stephen,[12] who recommended the use of morphine preoperatively in their discussions of anesthesia for tonsillectomy. The use of a strong opiate preoperatively, while certainly helping to reduce anxiety, and allowing for effective postoperative analgesia, has the theoretical and possibly real disadvantage of depressing respiratory function during operation. Such is more likely to be of concern when an insufflation technic is used in the management of the anesthesia. As witnessed by the results of this study, the administration of the mild analgesic, codeine, in the immediate postoperative period gives satisfactory analgesia without excessive depression either during the operative or postoperative period.

Summary

A study was carried out on 60 pediatric patients with the purpose of comparing the relative merits of three drugs: codeine, pentobarbital and placebo in terms of their ability to provide analgesia and to control restlessness and agitation following tonsillectomies. A "double-blind" technic was used whereby the nature of the medication was unknown to the individuals who administered the drugs as well as to the observers who judged the reaction of the patients.

Eighty per cent of the patients who received codeine were classified as quiet, where-

as only 30 and 35% respectively for pentobarbital and placebo were in this category. None of the children who received codeine became irrational following their return from the recovery room. Pentobarbital was seen to offer no advantage over the placebo in preventing a restless or an irrational postoperative course.

Side effects during the postoperative observation period were minimal with no clinical appearance of cardiovascular or respiratory depression. Vomiting was limited to transient episodes of retching in 3 patients following full recovery from anesthesia.

Codeine administered in the immediate postoperative period has proven to be an excellent analgesic and an effective prophylactic against excitement, delirium, and agitation following tonsillectomies in children.

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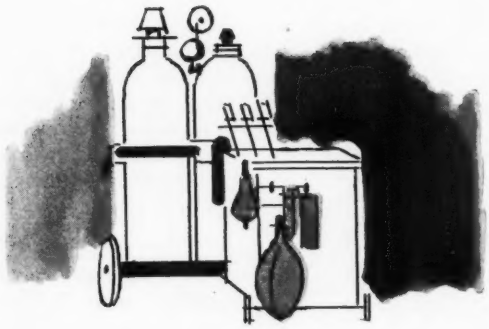

EDITORIAL

WHAT IS THE COURSE OF UNTREATED HYPERTENSION

As the physician contemplates the hundreds of thousands of dollars spent in research for new antihypertensive drugs by pharmaceutical houses, and similar amounts by patients for such drugs and in professional fees, he cannot help but wonder what the dividends may be in the ultimate result of the management of *primary* hypertension. Surely all doctors who have practiced medicine for several decades can name patient after patient whose "essential" hypertension has had an uncomplicated course over such a period. In undertaking the management of any disease it must be done within the perspective of the natural history of its course.

The Natural History of Primary Hypertension[1] therefore was selected as a title for editorial comment on this page somewhat over a year ago utilizing some of the published material of Dr. George Perera of Columbia University. Excluding malignant hypertension and that secondary to other disease, "benign" or primary hypertension as shown by Perera's studies presents certain characteristics. Thus, it is a disease having its onset in early adult life, is more common in women, and has an average duration, before secondary pathologic changes cause death, of two decades. Furthermore, he pointed to an uncomplicated course of disease for three quarters of its 20 year course, the patient finally dying from cardiac complications. (Necrotizing arteriolitis and cerebral vascular accidents are found uncommonly in the natural history of primary hypertension.) Perera also was quoted as demonstrating that though the average age at death is in the sixth decade, many patients live much longer and reach a normal life expectancy. It was also indicated that it had been shown that a high "floor" of diastolic pressure is more important as related to complications than minimal elevations of diastolic pressure.

At the end of this editorial comment last year it was remarked that such studies of the natural course of primary hypertension are important as a yardstick for us in two decades from now. That will be the time to test the effectiveness of antihypertensive therapy in terms of extension of life and diminution of the incidence and severity of its complications. (One might add if a sufficient number of patients will have taken pills continuously for twenty years!)

Now, in this issue, appears a paper on *Untreated Hypertension*[2] which reviews Perera's studies as well as other similar ones and points to additional considerations in this important clinical area which demands objective thinking and planning.

Pruitt emphasizes that the pathogenesis of primary hypertension is unrelated to the aging process and that its onset no later than the fifth decade demonstrates this. By contrast, hypertension developing after age 50 is usually of a secondary nature, emphasizing the doctor's responsibility in searching for a cause of the disease in such persons. However, in contrast to the peak of age of onset of primary hypertension between 30 and 40 years, the concentration of deaths due to complications lies between 50 and 60 years of age. Pruitt points out that the increasing severity of coronary sclerosis, as shown at necropsy, reaches a peak at 55 years followed by a plateau extending to age 85, indicating that this lesion is probably related more directly to the aging process than to hypertension. This and the rather uncommon deaths due to uremia and cerebrovascular disease emphasize that death among patients having primary hypertension "reflect directly not consequences of the underlying arteriolar disease, but rather, of the associated arterial disease, whereas malignant hypertension has consequences directly reflecting the effects of the arteriolar disease."

These facts pose the question of any accelerating influence hypertension may have on the pathogenesis of atherosclerosis. Pruitt considers this question both from clinical studies as well as animal experimentation. The results are far from uniform, but he believes that

1. Editorial: The Natural History of Primary Hypertension, South M.J. 53:99, 1960.

2. Pruitt, Raymond D.: Untreated Hypertension, South M.J. 54:378, 1961.

hypertension and atherosclerosis each may seem to aggravate the other, even if they arise from independent causes. The course of malignant hypertension is clearly favorably influenced by antihypertensive methods, but such a favorable influence has not been established for the treatment of primary hypertension. The question therefore stands whether antihypertensive treatment can influence the development of atherosclerosis which may end fatally. May it mean that the treatment of primary hypertension at an earlier date will prevent atherosclerosis or that more continuous control, free of recurring episodes of hypertension, will influence the development of arterial lesions?

Much careful and controlled study will be needed, and with prolonged observation, before the effectiveness of present-day treatment of primary hypertension may be evaluated.

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25 YEARS AGO

Sickle-Cell Anemia: A New Cause of Cor Pulmonale.*

"The history of joint pains, with or without fever, the presence of an enlarged heart, the finding of a systolic precordial or mitral murmur and the discovery of enlargement of the liver frequently lead to the diagnosis of rheumatic heart disease in cases of sickle-cell anemia. According to Anderson and Ware a cardiac murmur is present in 75% of the cases, enlargement of the liver, clinically in 53% and enlargement of the heart clinically in 48%. Joint pains occur at some time, often intermittently, in 51%. . . . Hamman has reported an interesting case of a Negro girl with sickle-cell anemia in which several excellent clinicians made the diagnosis of rheumatic heart disease, with failure, which was not verified by necropsy. Diggs and Ching state that, 'Clinically, organic heart disease is often suspected,'. . . .

"Although many patients with sickle-cell anemia die at a relatively early age of some intercurrent infection, particularly pneumonia and pulmonary tuberculosis, a fair number die apparently as the result of the anemia itself. It is our belief that cardiac failure is often a part of the terminal picture, as evidenced by enlargement and dilatation of the heart and passive congestion of the liver. Our experience with 2 cases leads us to believe that there is usually something other than the severe anemia producing the cardiac failure, namely, hypertension of the lesser circulation due to numerous occlusions of the medium-sized and small pulmonary arteries with subsequent hypertrophy and failure of the right heart.

"Cyanosis was not observed during life in either of the cases here reported. In this respect the cases did not present the typical picture of right heart failure known as Ayerza's syndrome. There is a striking difference, however, between the ordinary case of Ayerza's syndrome and the cardiac picture in sickle-cell anemia, namely that in the one there is polycythemia and in the other there is usually severe anemia. Also, the usual case of cor pulmonale due to pulmonary arteriolar sclerosis is one in which dyspnea has occurred for months or years before death. The patient with severe sickle-cell anemia, however, dies usually before he can develop the full-blown picture of chronic right heart failure. . . .

"Summary and Conclusions.

"The cause of the right heart strain in the first case was thrombotic occlusions of the small and medium-sized arteries of the lungs, with organization and canalization of discrete thrombi which had formed from time to time. The heart failure was apparently precipitated by a final crop of fresh thromboses. The cause of the right heart failure in the second case was thickening of the walls of the small and medium-sized arteries and the arterioles of the lungs with reduction in their lumens, but thromboses were not present in the tissue studied.

"The absence of cyanosis is probably explained by the severe anemia, which prevents sufficient concentration of reduced hemoglobin to produce the picture of Ayerza's syndrome.

"Right heart failure due to vascular changes in the lungs must be common in cases of sickle-cell anemia, since many of the patients have enlarged hearts, systolic murmurs and hepatomegaly.

"Capillary stasis due to distortion and agglutination of erythrocytes is probably the essential factor in the changes described in the small arteries."

*Yater, W. M., and Hansmann, G. H.: Sickle-Cell Anemia: A New Cause of Cor Pulmonale. Report of Two Cases with Numerous Disseminated Occlusions of the Small Pulmonary Arteries, Am. J. M. Sc. 191:474, 1936.

Welcome to Big "D"

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Dallas, Texas November 6-9, 1961

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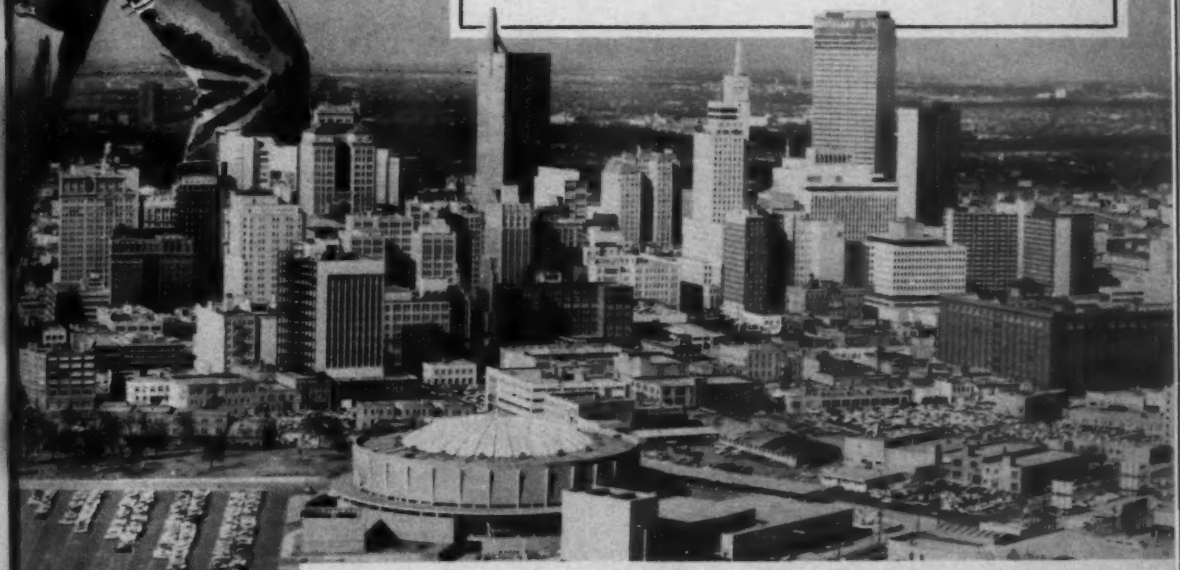

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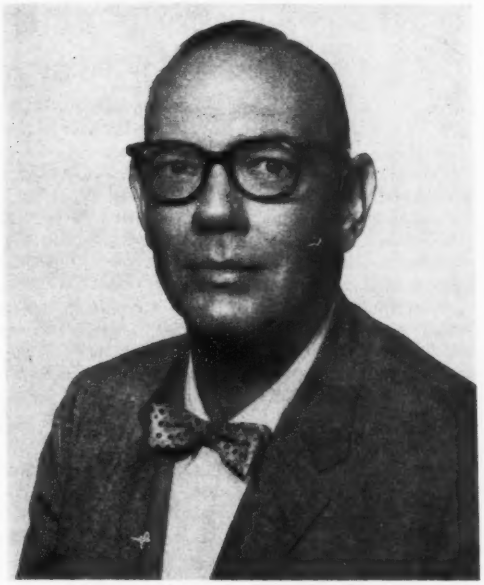
In Memoriam

Dr. Milton M. Hattaway

1911-1961



Milton M. Hattaway, M.D.

Dr. Milton M. Hattaway, New Orleans, Louisiana, passed away Wednesday, March 8, after a brief illness. Dr. Hattaway had been admitted to Baptist Hospital the previous week for a heart ailment. He was fifty years of age.

Dr. Hattaway, born February 18, 1911, in Nobel, Louisiana, was reared in North Louisiana and was graduated from Campti High School. He attended Centenary College in Shreveport, where he received his B.S. degree in 1930. He obtained his medical education at Tulane University School of Medicine, and following his graduation in 1934, interned at the Southern Baptist Hospital, 1934-1935. He was a resident in surgery at the same hospital in 1935-36. Dr. Hattaway entered practice in New Orleans in 1936 and had resided there for the past 31 years. In 1942 he entered the United States Navy Medical Corps and served as a Lieutenant Commander. Upon completion of his tour of duty in 1946 he returned to New Orleans and had practiced there continuously since that time.

Dr. Hattaway became a member of Southern Medical Association in 1937. Since that time he had been an active supporter of the Association and had served as Councilor from Louisiana since 1959.

In addition to Southern Medical, he was a member of the Orleans Parish Medical Society, the Louisiana State Medical Society, American Medical Association, Louisiana Surgical Association, and Treasurer of the New Orleans Graduate Medical Assembly.

Dr. Hattaway resided at 3 Audubon Boulevard, and is survived by his wife, the former Lewis Ann Berry, a daughter, Marcia Milancy, two sons, Michael Medwin and Jonathan Louis, two sisters and two brothers.

Dr. Hattaway will be missed greatly by his many friends and associates in Southern Medical.

SOUTHERN MEDICAL NEWS

State News Items

The American Medical Association is sponsoring two regional medicolegal conferences in April. One meeting will be held in Louisville, Kentucky, on April 14 and 15, at the Kentucky Hotel, and the other in New York City, on April 28 and 29, at the Statler Hilton Hotel. The program will be of interest to doctors and lawyers alike. Some of the subjects to be included are: Medical Expert Testimony and the Status of Medicolegal Relations. The registration fee for each conference will be $5.00, which includes the cost of a luncheon and any proceedings of the meeting that may be published. For any further information contact C. Joseph Stetler, Director, Legal and Socio-Economic Division, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

The Fifty Year Club of American Medicine, organized in 1960, will hold its second meeting June 25-30, 1961, during the Annual Meeting of the American Medical Association in New York City. This group was organized as a social function to "honor physicians who have been in the study and practice of medicine fifty years or more." Dr. J. H. McCurry, Cash, Arkansas, organizer, is Secretary of the Club.

The Eighth Annual Convention of the National Geriatrics Society will be held May 1-4, 1961, at the St. Francis Hotel in San Francisco. Scientific, technical and business sessions are planned, as well as group tours, a banquet and other social events. For further information contact the National Geriatrics Society, 5 Park Towne South, Philadelphia 30, Pennsylvania.

ALABAMA

Dr. Marshall Eskridge, Mobile, is Secretary-Treasurer of the Southern Radiological Conference.

Officers of the Alabama Chapter of the American College of Surgeons are Dr. James P. Collier, Tuscaloosa, President; Dr. E. Vernon Stabler, Greenville, President-Elect; Dr. T. Brannon Hubbard, Montgomery, Secretary-Treasurer; and Dr. John W. Donald, Mobile, Executive Council member.

The Birmingham Baptist Hospitals medical staff has elected new officers: Dr. J. L. Parsons, President; Dr. William Warrick, Vice-President; and Dr. Gordon Ross, Secretary. All are of Birmingham.

ARKANSAS

Dr. T. D. Norman, formerly of the pathology staff at the University of Arkansas Medical Center, has returned as head of the Department of Pathology. He has been serving as Associate Professor of Pathology at Tulane University, New Orleans, Louisiana.

New officers of the Ouachita County Medical Society are Dr. W. H. Pruitt, President; Dr. R. C. Lewis, President-Elect; and Dr. R. B. Robins, Secretary, all of Camden.

Dr. Paul Gray, Batesville, is President, and Dr. Alfred Hathcock, Batesville, Secretary, of the Second Councilor District of the Arkansas Medical Society.

The Pulaski County Medical Society has elected the following officers: Dr. John William Smith, President; Dr. John McCollough Smith, President-Elect; Dr. Guy R. Farris, Vice-President; and Dr. Carl E. Wenger, Recording Secretary, all of Little Rock.

DISTRICT OF COLUMBIA

Dr. Lawrence G. Christianson has been appointed Assistant Director of Medical Service for the Veterans Administration in Washington.

Officers of the Washington Hospital Center's medical staff are Dr. Edgar W. Davis, President; Dr. Theodore J. Abernethy, First Vice-President; Dr. Thomas W. Mattingly, Second Vice-President; Dr. Francis L. Wenger, Secretary; Dr. Paul R. Wilner, Assistant Secretary; and Dr. Garnet W. Ault, Treasurer.

Dr. Herbert P. Ramsey, Chairman of the Hospital Advisory Council to the District of Columbia, has been named Chairman of the Physicians' Advisory Committee to the Greater Southeast Community Hospital.

Capt. Joseph P. Pollard, MC, USN, has assumed the position of Special Assistant for Medical and Allied Sciences at the Office of Naval Research.

Officers of the medical staff of Children's Hospital are: Dr. John A. Washington, Chairman; Dr. C. Edwin McNamara, Vice-Chairman; and Dr. Richard H. Todd, Secretary-Treasurer.

FLORIDA

Dr. Walter W. Sackett, Jr., Miami, has been elected to the Board of Trustees of the University of Miami. He has just completed a term as President of the Alumni Association of the same university.

The following Miami physicians are officers of the Greater Miami Radiological Society: Dr. George P. Daurelle, President; Dr. Donald H. Altman, Vice-President; and Dr. Carl E. Balli, Secretary-Treasurer.

Dr. Dewitt C. Daughtry, Miami, is the new President of the Southern Thoracic Surgical Association.

Dr. Jean Jones Perdue, Miami, recently installed as President of the Heart Association of Greater Miami, is the first woman to hold this position.

GEORGIA

The Atlanta Society of Pathologists is conducting a seminar on pediatric pathology at the Academy of Medicine, 875 West Peachtree Street, Atlanta, on Sunday, April 9, 1961. Please address all correspondence and application to Dr. Heinz Bauer, Department of Pathology, Emory University School of Medicine, Atlanta 22, Georgia.

Dr. A. Hamblin Letton, Atlanta, has received the Aven Citizenship Award for 1960, given annually by Dr. and Mrs. Carl C. Aven to "recognize outstanding citizenship service and to stimulate interest among physicians to accept civic responsibilities."

KENTUCKY

Dr. Harry C. Denham, Maysville, was elected a Director of the State National Bank of Maysville. Another Maysville physician, Dr. W. H. Cartmell, was renamed to the Board of Directors of the Bank of Maysville.

Dr. B. N. Pittenger, Paris, has been elected President of the National Bank and Trust Company of Paris.

Dr. Jesse W. Page has become associated with the Fuller-Morgan Clinic in Mayfield.

Dr. Earl Douglas Rees has joined the faculty of the University of Kentucky Medical Center as Assistant Professor of Medicine.

LOUISIANA

The Tulane University School of Medicine has created the Edgar Burns Visiting Professorship in Urology in honor of the urologist who served for 12 years as Head of the Division of Urology at Tulane. The first incumbent of the professorship is Dr. Hartwell Harrison, Professor of Genito-Urinary Surgery at Harvard Medical School.

Dr. John S. Salatich, New Orleans, has been appointed to the Advisory Committee of the Bank of Louisiana in New Orleans.

MARYLAND

The 163rd Annual Meeting of the Medical and Chirurgical Faculty of the State of Maryland will be held April 26-28, 1961. For further information contact the Medical and Chirurgical Faculty, 1211 Cathedral Street, Baltimore 1, Maryland.

Dr. Seymour S. Kety, Bethesda, has been appointed Professor of Psychiatry and Director of the Department of Psychiatry at the John Hopkins University School of Medicine and psychiatrist-in-chief of the John Hopkins Hospital.

MISSOURI

New appointments at the University of Missouri Medical Center include Dr. J. Modlin, Professor of Surgery and Chairman of the Department of Surgery; Dr. Edward B. Shires, Clinical Associate Professor of Medicine in the Department of Medicine; Dr. Robert Earl Froelich, Assistant Professor in the Department of Psychiatry; and Drs. Don R. Sipes and Carl C. Pearman, both Assistant Instructors in Obstetrics and Gynecology and first year Residents in Obstetrics and Gynecology.

NORTH CAROLINA

Two professors at Duke University Medical Center have received new honors. Dr. Roger D. Baker, Professor of Pathology at the Center and Chief of the Laboratory Service at the Veterans Administration Hospital, has been named Head of the American Board of Pathology. Dr. Henry D. McIntosh, Associate Professor of Medicine, has been elected Vice-Chairman of the southern section of the American Federation for Clinical Research.

Dr. Joan V. Williams, Instructor in Psychology in the Department of Psychiatry at the University of North Carolina School of Medicine, has been promoted to Assistant Professor.

OKLAHOMA

New faculty appointments at the University of Oklahoma School of Medicine have been announced. Dr. George J. Friou is Associate Professor of Medicine, and Dr. Bernard Horn, Instructor in Anesthesiology. Appointed to the part-time teaching staff were Dr. Robert Lewis Kramer, Clinical Assistant in Ophthalmology, and Dr. Vernon G. Ward, Clinical Assistant in Medicine.

Dr. Kirk T. Mosley, Oklahoma Commissioner of Health, has announced the appointment of the following County Superintendents of Health: Dr. Clyde M. Bloss, Holdenville, for Hughes County; Dr. Joan K. Kiett, Altus, for Jackson County; and Dr. Jerry E. King, Stigler, for Haskell County.

Dr. William N. Weaver, Muskogee, has been named to the State Board of Health.

SOUTH CAROLINA

The 113th Annual Meeting of the South Carolina Medical Association will be held at the Francis Marion Hotel, Charleston, S. C., April 25-27, 1961. For further information contact Dr. J. I. Waring, 82 Rutledge Avenue, Charleston.

Dr. E. A. Dreskin, Greenville, has been re-elected President of the South Carolina Society of Pathologists.

Dr. Peter C. Gazes has become associated with the full-time faculty at the Medical College of South Carolina, specializing in cardiovascular diseases.

Continued on page 62

INSTRUCTIONS TO CONTRIBUTORS

Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Because of lack of space, it is necessary to limit the number of bibliographic references to twenty. Footnotes and references should conform to the following style:

1. Doe, J. E.: What You Should Know about It, South. M. J. 50:711, 1950.

Illustrations: Black and white glossy prints, preferably 5 by 7 inches, and drawings in India ink on white paper are required. The author's name, number and indication of top, if doubtful, should be attached. Necessary plates not exceeding six, or one and a half pages, will be furnished by the Journal.

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Business Address: All correspondence related to membership, subscriptions, advertising, and other business should be addressed to the Southern Medical Association, 2601 Highland Avenue, Birmingham 5, Alabama.

BOOK REVIEWS

Colloquia on Ageing, Vol. 4. The Lifespan of Animals

Edited by G. E. W. Wolstenholme, and Maeve O'Connor. Ciba Foundation. 311 pages, illustrated. Boston: Little, Brown & Company, 1959. Price $9.50.

This pleasant little volume, the fifth and last in the CIBA series on aging, presents original researches and thinking on matters of intrinsic interest to the ecologist and actuarian but of fundamental interest to those investigators concerned with the larger issues of their labors, particularly issues of evolution and adaptive mechanisms. Unlike its predecessors which dealt with phenomena of tissues, organs, and systems, this volume delves into features of the population or even of the species as they characterize the aging process. In all, this book will make for rewarding reading for those researchers titillated by new data and other than the accustomed technics; it will make for refreshing reading for the laity enthused by doings and doers.

Cutaneous Manifestations of the Reticuloendothelial Granulomas

Edited by Samuel M. Bluefarb, M.D. American Lecture Series. 436 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1960. Price $14.50.

The fourth in a series pertaining to cutaneous manifestations of all the diseases of the reticuloendothelial system edited by Dr. Bluefarb, this monograph provides a thorough and quite well-illustrated documentation of the lipidoses, reticuloendothelioses, sarcoidosis and mastocytosis (urticaria pigmentosa). Dr. Frederick Urbach's review of the lipidoses, including Niemann-Pick and Gaucher's diseases, is representative of over 30 years of productive interest in these disorders. It is unfortunate that an illustration of the pingueculae of Gaucher's could not have been included. Dr. Bluefarb emphasizes the continuum between Letter-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma. Three authors jointly provide the shortest section of the book on sarcoid. The relative paucity of dermatologic illustrations in this chapter, in contrast to the other sections, does not do complete justice to the variability of cutaneous sarcoid. The occasional massive, lymphoma-like cervical and axillary adenopathy seen in this disease should have deserved recognition. The largest chapter of this volume, comprising 169 of the 436 pages of text, is the most complete and authoritative assembly of facts and illustrations on mastocytosis known to date by the reviewer and is based on an exhaustive bibliography. Not too many years ago considered a benign curiosity seen essentially in children, the systemic nature of this disease has become distinct in recent years, capable of truly malignant potential from which much has been learned of mast-cell function. This has been summarized and discussed so extensively by Drs. Sagher and Even-Paz that this chapter will compel the attention of workers in many fields.

The emphasis throughout the book, as indicated by the title, has been dermatologic, and this volume will be of pronounced value to those with such a primary interest. Such a unique accumulation of information and illustrations will, however, be of more than passing interest to those in general medicine.

Fellowship of Surgeons

By Loyal Davis, M.D. 507 pages. Springfield, Ill.: Charles C. Thomas, Publisher, 1959. Price $10.50.

The history of the American College of Surgeons from its founding to current times is well documented in this volume. No punches are pulled in the recounting of the organization's own internecine strife and the criticism directed at the College from other organzations and individuals is given in detail. Throughout all of its organizational vicissitudes the directing hand of Franklin Martin, its founder, is clearly evident.

Not only is the volume an excellent commentary on many biographical features of such surgical giants as Murphy, Finney, Graham, Ravdin, the Mayos, Crile, and others, it offers a detailed account of the struggle for the abolition of fee-splitting, the elevation of standards of surgical training, and the improvements in hospital services leading to hospital accreditation.

This book will be of real value to those interested in the history of American surgery and, in particular, to all Fellows of the American College of Surgeons. The contributions of the author to the College throughout the years is modestly concealed.

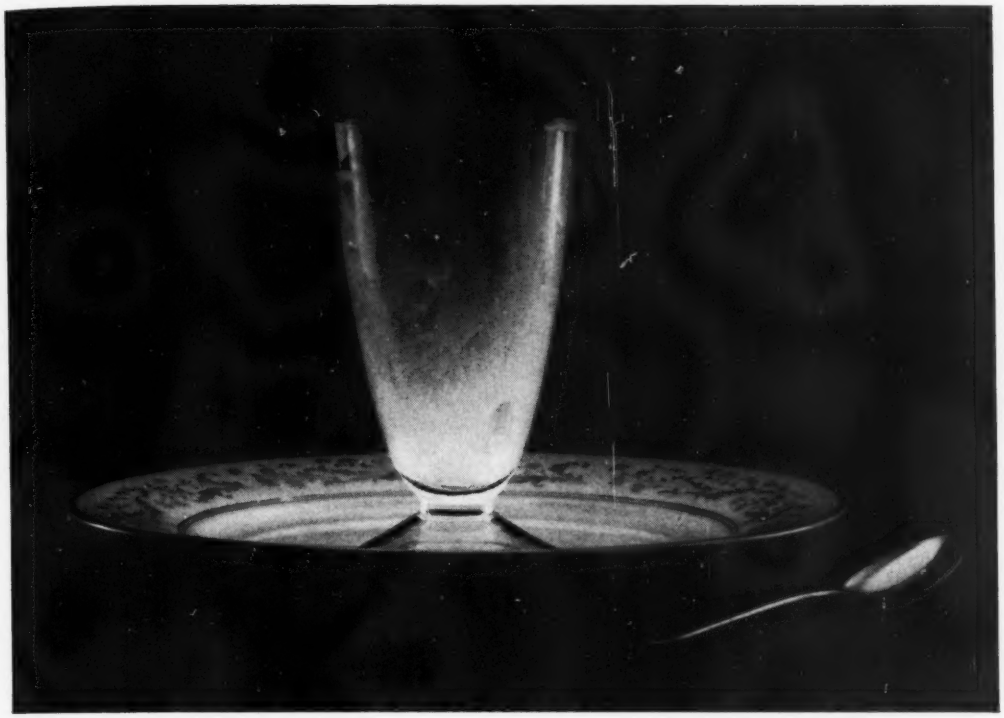
Haemopoiesis. Cell Production and Its Regulation. Ciba Foundation Symposium

Edited by G. E. W. Wolstenholme and Maeve O'Connor. 466 pages. Boston: Little, Brown & Company, 1960. Price $11.00.

This volume constitutes a reproduction of papers presented at the Ciba Foundation Symposium on Haemopoiesis held in February 1960. The book is not a summary or review of work to date, but presents recent work on the lymphomyeloid complex and the nature of the primitive multipotential cell which some call the stem cell and Yoffey feels is the small lymphocyte. Various new technics are described, such as radioautography employing tritiated thymidine labeled lymphocytes to trace their physiology particularly in relation to the thymus gland.

Recent work in erythropoietin is presented. Gordon presents his method of adsorbing urinary erythropoietin activity prior to concentrating it for study. Linman presents a summary of his work with the late Dr. Frank Bethell on two biologically different erythropoietic plasma activities separated by thermostability and ether solubility. Jacobson and Goldwasser and Gurney present their technic of sensitizing rats to erythropoietin for assay purposes by transfusing them to polycythemic levels.

This is not a book for casual reading and presupposes a background in the area of blood cell formation. Its intent is to make available the information contained in the papers to those with special interests in the field. Of great interest are the discussions, printed in full, following each paper in which results are compared and evaluated and opinions freely expressed in a less formal atmosphere.



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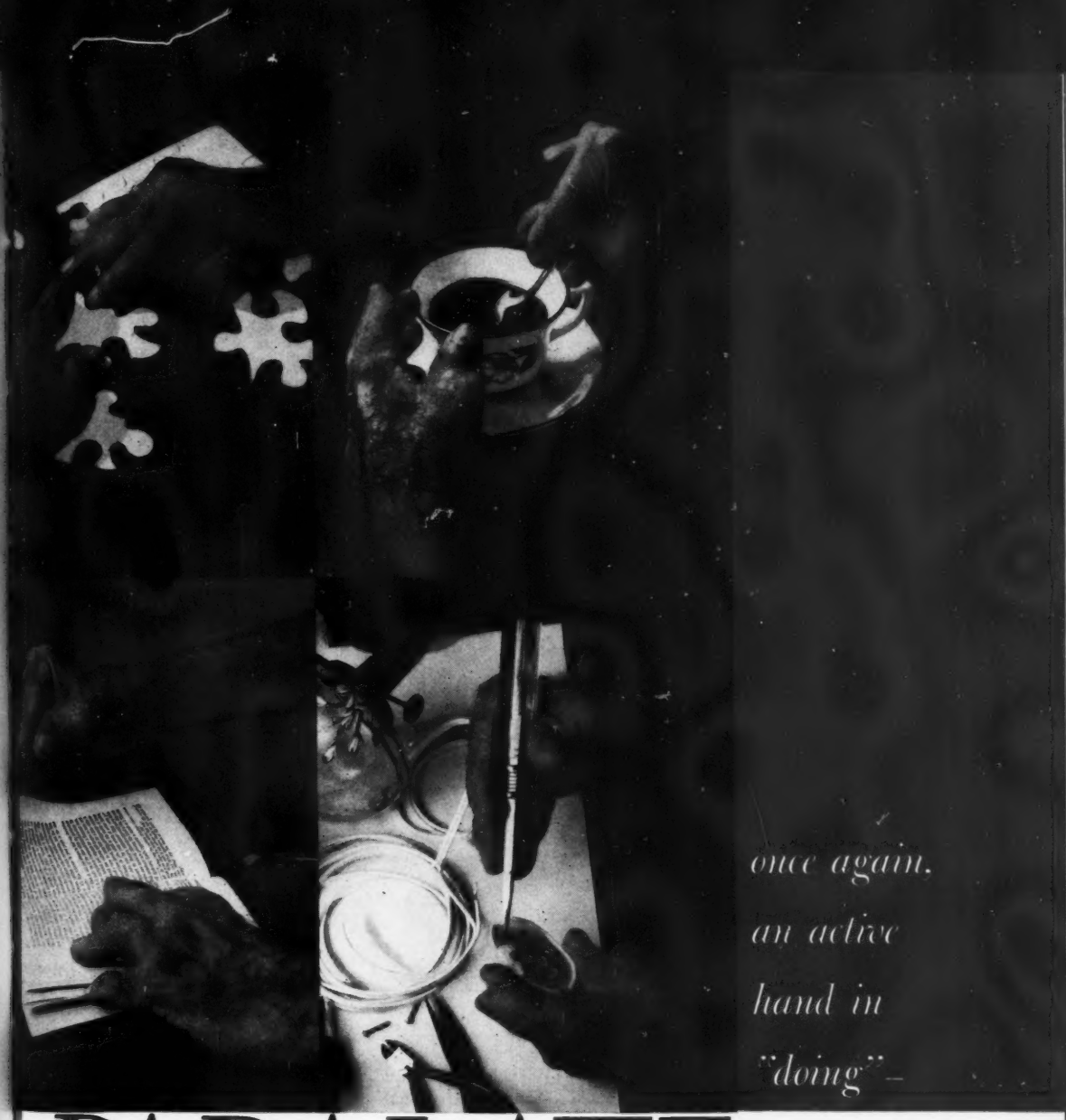

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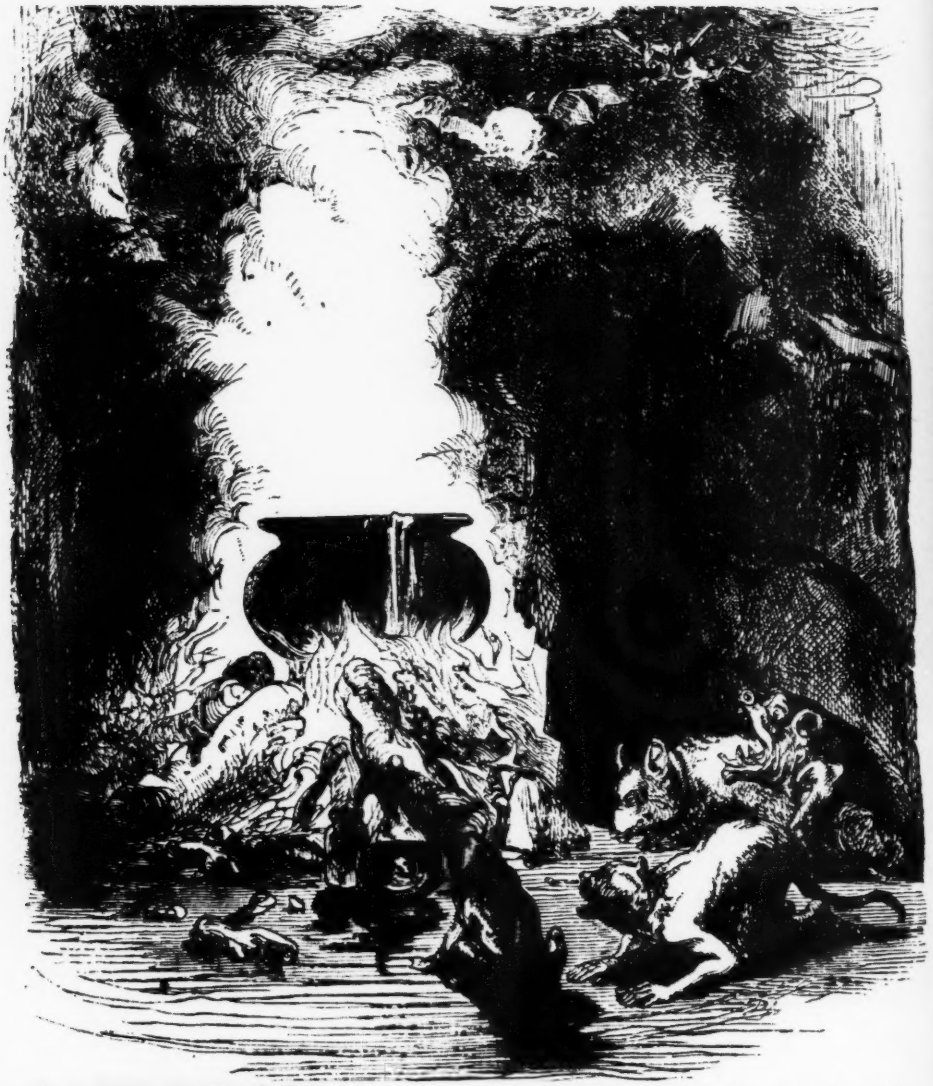

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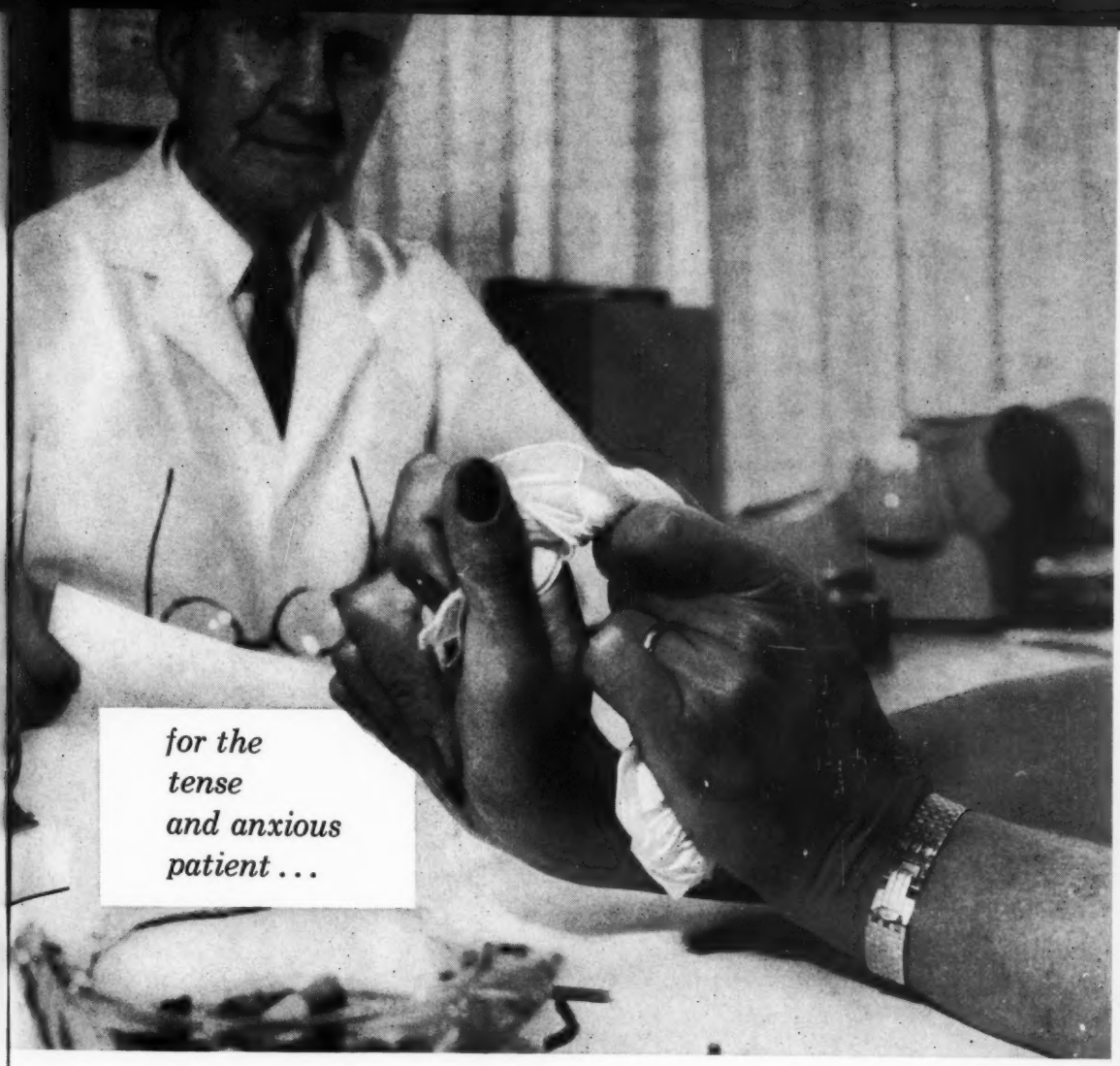

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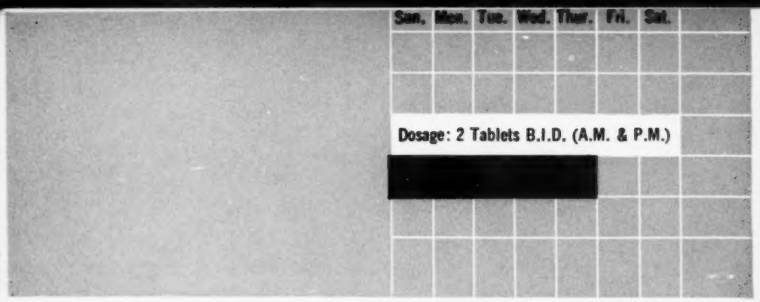
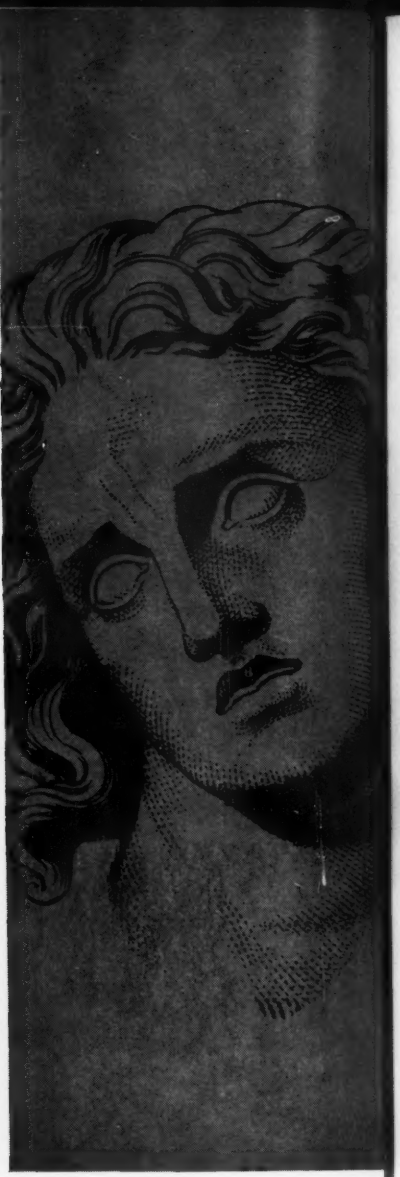


in premenstrual tension only neo Bromth® treats the whole syndrome



It was the introduction of neo Bromth several years ago that created such widespread interest in the premenstrual syndrome—because of neo Bromth's specific ability to prevent the development of the condition in the first place.

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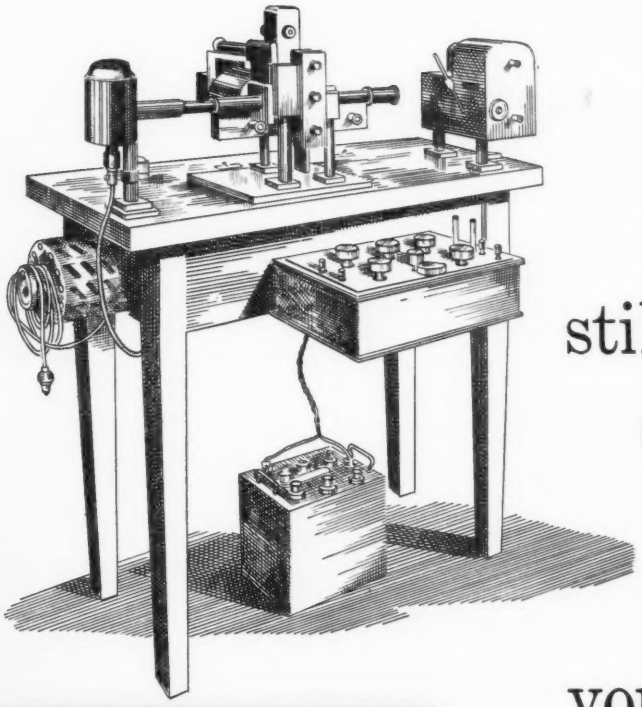

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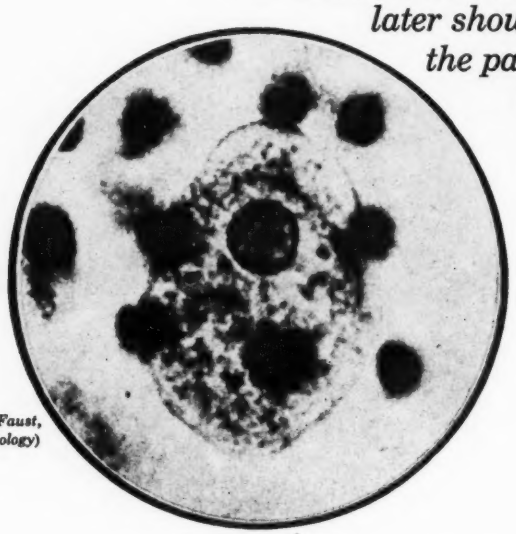

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No. of Patients Examined	No. of Controls	No. Positive Before Treatment	No. Positive After First Course of Treatment
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1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic Endamoeba histolytica Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). (To be published in Am. J. Gastroenterol., October, 1960.)

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References: 1. Curran, T. R., and Phelps, D. K.: Am. Pract. & Dig. Treat. *11:* 617, 1960. 2. Levy, S.: J.A.M.A. *153:* 1260, 1953. 3. Connolly, R.: W. Va. Med. J. *56:* 263, 1960.

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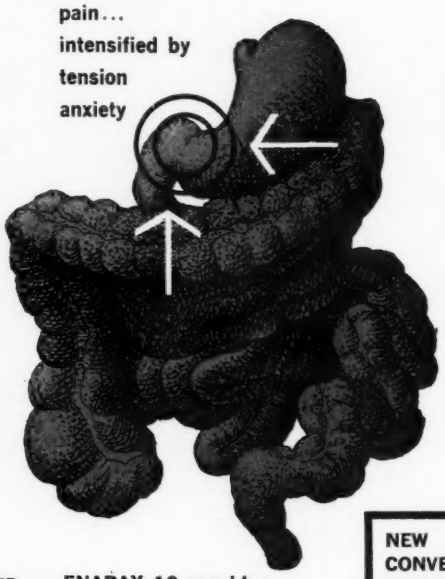
double trouble of the g.i. tract?

spasm
hyperacidity
pain...
intensified by
tension
anxiety



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References: 1. Hock, C. W.: Am. J. Gastroenterol. 34:293 (Sept.) 1960. 2. Leming, B. H., Jr.: Clin. Med. 6:423 (Mar.) 1959. 3. Data in Roerig Medical Department files.

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REFERENCES:

1. Scherbel, A. L.; Schuchter, S. L., and Harrison, J. W.: Cleveland Clin. Quart. 24:98, April, 1957.
2. Waine, Hans: Arthritis, rheumatoid, in Conn, H. F.: Current Therapy 1959, Philadelphia, W. B. Saunders Co., 1959, p. 565.

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One pharmaceutical research executive points up the importance of failures as guideposts to success in the search for new or improved drugs when he says:

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The pharmaceutical industry's investment in research has been growing much faster than the industry itself. Last year the prescription drug companies spent a record $197 million for research, a five-fold increase in the space of ten years. Such an investment is possible, of course, only when there are profits. • This growth in privately financed research has sent the volume of laboratory failures soaring. For two years in a row the pharmaceutical industry has tested more than 100,000 substances in the search for new medicines. Fewer than two per cent showed enough promise for clinical testing. Only a handful will ever be sold as prescription drugs. The odds against finding a product with therapeutic value probably exceeded 2000-to-1. • But year by year, as the failures mount, the successes also increase, putting new or improved medications at the disposal of the medical profession. And the public benefits through better health, specific cures, shorter hospitalization, longer lives. • This is only one part of the massive assault on disease that engages the health team headed by the medical profession and embracing hospitals, nurses, pharmacists, technicians, and colleges. It is an effort that could only take place in a society which encourages individual freedom and guarantees incentives to freedom of enterprise.

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1. Beck, C., *et al.*: Clin. Med. 7:519, 1960. 2. Teitel, L. H., *et al.*: Indust. Med. 29:150, 1960. 3. Billow, B. W., *et al.*: Southwestern Med. 41:286, 1960. 4. Clinical Reports to the Medical Department, Armour Pharmaceutical Company, 1960. 5. Taub, S. J.: Clin. Med. 7: 2575, 1960.

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Chymoral is an ORAL anti-inflammatory enzyme tablet specifically formulated for intestinal absorption. Each tablet provides enzymatic activity, equivalent to 50,000 Armour Units, supplied by a purified concentrate which has specific trypsin and chymotrypsin activity in a ratio of approximately six to one. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac or renal origin; hastens absorption of blood and lymph extravasates; helps to liquefy thick tenacious mucous secretions; improves regional circulation; promotes healing; reduces pain. INDICATIONS: Chymoral is indicated in respiratory conditions such as asthma, bronchitis, rhinitis, sinusitis; in accidental trauma to speed absorption of hematoma, bruises, and contusions; in inflammatory dermatoses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologic conditions such as pelvic inflammatory disease and mastitis; in obstetrics as episiotomies and breast engorgement; in surgical procedures as biopsies, hernia repairs, hemorrhoidectomies, mammectomies, phlebitis and thrombophlebitis; in genitourinary disorders as epididymitis, orchitis and prostatitis; in dental and oral surgery as fractures of the mandible or maxilla, difficult or multiple extractions, and alveolectomies. CONTRAINDICATIONS: None known. INCOMPATIBILITIES: None known. Antibiotics as well as generally accepted measures may be coadministered. SIDE EFFECTS: Mild gastric upsets, rarely encountered. DOSAGE: Recommended initial dose is two tablets q.i.d.; one tablet q.i.d. for maintenance. SUPPLIED: Bottles of 48 tablets.

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LOCUM TENENS WANTED—Large General Practice, West Virginia. $30.00 day plus room. Meals not furnished. Temporary license arranged. Contact AK, c/o SMJ.

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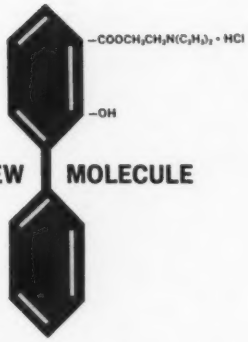

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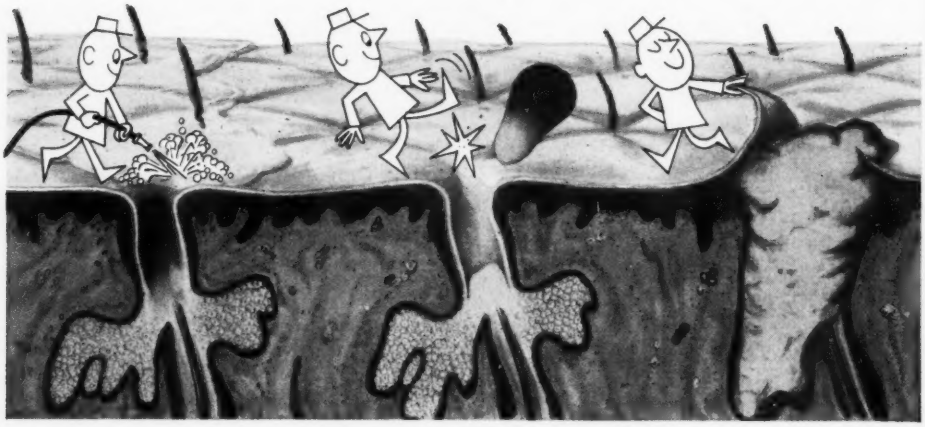
Supplied: 4 oz. white plastic squeeze bottle. RX only.

References: 1. Lubowe, I. I.: Treatment of Seborrhea Capitis and Associated Diseases, Southern Medical Jl., April, 1961. 2. Pharmacology Research Inc., Darby, Pennsylvania. 3. Gant, J. Q.: To be published. 4. Lorant, E.: To be published. 5. Burks, J. W.: To be published. *Literature and samples available to physicians on request.*

Wampole Laboratories, Stamford, Conn. 142WS



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degreases the skin
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dries and peels the skin

Patients like Fostex because it's so easy to use. Instead of using soap, they simply wash acne skin with Fostex Cream or Fostex Cake 2 to 4 times daily.

Fostex contains: Sebulytic® base (unique, penetrating, surface-active combination of soapless cleansers and wetting agents*) with remarkable antiseborrheic, keratolytic and antibacterial actions . . . enhanced by micropulverized sulfur 2%, salicylic acid 2% and hexachlorophene 1%.

*sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate.

Fostex Cream and Fostex Cake are interchangeable for therapeutic washing of the skin. Fostex Cream is approximately twice as drying as Fostex Cake. Supplied: Fostex Cake—bar form. Fostex Cream—4.5 oz. jars. Also used as a therapeutic shampoo in dandruff and oily scalp.

And . . . since continuous 24-hour drying and peeling of acne skin is essential, FOSTRIL (a new, flesh-tinted drying lotion) should be used once or twice daily in addition to Fostex therapeutic washings. Fostril® contains Liposec® (polyoxyethylene lauryl ether), a new, surface-active drying agent used for the first time in acne treatment. This agent, with 2% micropulverized sulfur and a zinc oxide, talc and bentonite base, provides Fostril with excellent drying properties. Fostril also contains 1% hexachlorophene.

Available: Fostril, 1½ oz. tubes. Fostril-HC (¼% hydrocortisone) 25 gm. tubes.

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Hydrocortisone in a sterile, slightly acid, aqueous suspension ..... 10 mg.
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Literature available on request.

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Continued from page 463

TENNESSEE

Dr. Harold Thomas McIver, Jackson, has been elected Chief of Staff of the Jackson-Madison County General Hospital. Assistant Chief will be Dr. Baker Hubbard, also of Jackson.

The following Paris physicians are officers of the Henry County Medical Society: Dr. John E. Neumann, President; Dr. W. G. Rhea, Vice-President; and Dr. Kenneth Ross, Secretary-Treasurer.

Dr. Alfred P. Rogers, Chattanooga, has been certified as a Diplomate of the American Board of Surgery.

Dr. John H. Burkhart, Knoxville, has been re-elected President of the Knoxville City School Board.

Bristol physicians who are newly installed officers of the medical staff of the Bristol Memorial Hospital are Dr. Homer Williams, Chief of Staff; Dr. Bennett Y. Cowan, Vice-Chief of Staff; Dr. William Johnson, Secretary; Dr. Robert Repass, Chief of Surgical Section; Dr. Walter R. Gaylor, Chief of Medical Section; Dr. Sidney Whittaker, Chief of Obstetrics and Pediatrics Section.

Dr. G. H. Berryhill, Jackson, was named Jackson's "Man of the Year for 1960" by the Jackson Exchange Club.

Dr. Robert Jones, Dyersburg, has joined the staff of the Dyer Clinic.

Continued on page 64

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NEOMYCIN—actively bactericidal against a wide range of gram-negative intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

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Complete Clinical and
Anatomical Pathology Services
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CONSULTATIONS WELCOMED

Continued from page 62

Dr. Arthur W. Green, Memphis, has been promoted to the rank of Colonel in the 306th Field Hospital, United States Army Reserve Unit at Memphis.

Dr. John T. Mason, McMinnville, is President of the Middle Tennessee Medical Association. Re-elected Secretary was Dr. Greer Ricketson, Nashville.

The following Knoxville physicians are officers of the medical staff of the Baptist Hospital in Knoxville: Dr. George A. Zirkle, Jr., Chief of Staff; Dr. John E. Kesterson, Vice-Chief; and Dr. William A. Gardner, Secretary. Elected to other posts were Dr. E. C. Idol, Chief of General Practice; Dr. Walter H. Benedict, Chief of Surgery; Dr. K. A. O'Connor, Chief of Obstetrics and Gynecology; and Dr. Daniel Davis, Chief of Medicine.

Dr. Pervis Milnor, Jr., Memphis, has been elected Chief of the medical staff of the Memphis Baptist Hospital.

Dr. Henry Callaway, Jr., Maryville, has been appointed to the active medical staff of Blount Memorial Hospital.

TEXAS

Dr. R. H. Bell, Palestine, is President of the Fourth District Chapter of Texas of the American College of Surgeons.

Dr. Thomas B. Bond, Fort Worth, was recently presented with the Gold Medal of the Radiological So-

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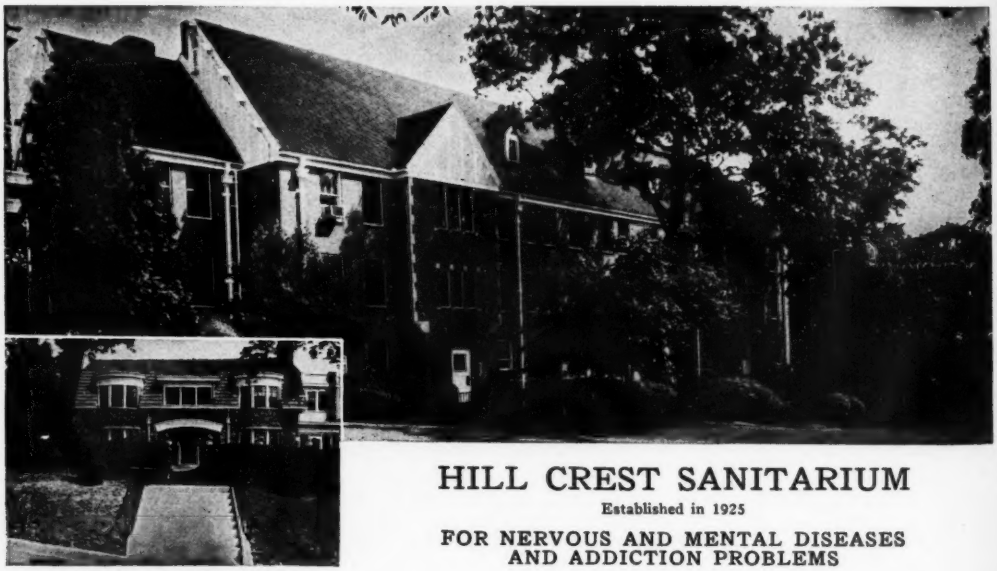

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LONTABS® (long-acting tablets CIBA)

new Forhistal® rated better than previous therapy in 7 cases out of 10

CIBA
SUMMIT, NEW JERSEY

2/2910MK

Continued from page 64

ciety of North America the Society's highest honor, in recognition of outstanding contributions to medicine.

Dr. Arnold M. Weissler has been appointed Assistant Director of the Cardiovascular Research Laboratory and Assistant Professor of Internal Medicine at the University of Texas Medical Branch in Galveston.

Dr. Paul Geers, Whitewright, was recently elected President of the Whitewright Chamber of Commerce.

Dr. May Owen, Fort Worth, President of the Texas Medical Association, was recently named a Headliner by the *Fort Worth Press.*

VIRGINIA

Dr. Oscar Swineford, Jr., member of the medical faculty at the University of Virginia for more than 30 years, has been honored by the establishment of the Oscar Swineford Allergy Fund. Income from the fund will be used by the dean of the medical school "to promote the graduate or undergraduate teaching of allergy." Dr. Swineford has served as Chairman of the Section on Allergy of the Southern Medical Association.

The Medical Society of Virginia has the following new members: Dr. Charles C. Ashby, Dinwiddie; Dr. Rogelio M. Borrell, Williamsburg; Dr. Max Carlton Feinman, Lynchburg; Dr. Albert A. Fratrick, Appomattox; Dr. Herbert C. Jones, Jr., Charlottesville; Dr. John G. Novak, Lynchburg; Dr. Ramon B. Perez, Wise; and Drs. Bruce C. Banning, Robert G. Bullock, and Reginald Paul McManus, all of Arlington.

WEST VIRGINIA

New faculty appointments at the West Virginia School of Medicine include Dr. Barbara Jones, Assistant Professor of Pediatrics; and Dr. Charles E. Andrews, Associate Professor of Medicine.

Dr. Margaret T. Ross, Charleston, has been appointed consulting psychiatrist for the Kanawha County School system on a part-time basis.

Dr. Fred A. Kennedy, Hopemont, has been named Superintendent of the Hopemont Sanitarium.

New members of the West Virginia State Medical Association are Drs. Harry A. Jackson and John J. Schaefer, both of Charleston.

Officers of the Kanawha Medical Society are Dr. W. B. Rossman, President; Dr. Robert C. Bock, Vice-President; and Dr. A. B. Curry Ellison, Secretary-Treasurer, all of Charleston.

Dr. Henry F. Warden, Jr., Bluefield, is President of the Mercer County Medical Society. Dr. Joe McCary, Princeton, is Vice-President; and Dr. John J. Mahood, Bluefield, is Secretary-Treasurer.

The following Morgantown physicians are officers of the Monongalia County Medical Society: Dr. R. J. Nottingham, President; Dr. C. A. Smith, Vice-President; Dr. C. C. Romine, Secretary; and Dr. John H. Trotter, Treasurer.

Drs. Ward Wylie and Mario Cardenas, both of Mullens, were elected President and Secretary-Treasurer, respectively, of the Wyoming County Medical Society.

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Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. **USUAL DOSAGE: 1 TABLET Q.I.D.**

The muscle relaxant with an independent pain-relieving action

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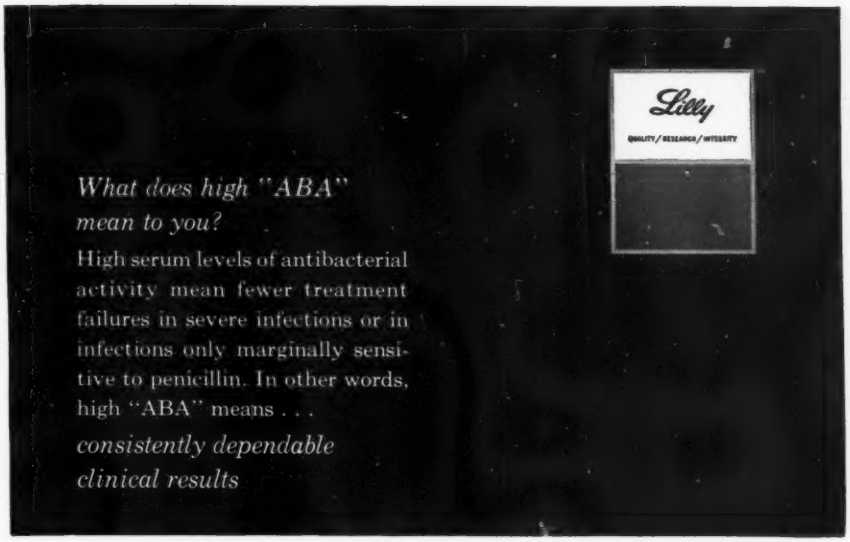

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References

1. McCarthy, C. G., and Finland, M.: Absorption and Excretion of Four Penicillins, New England J. Med., *263*:315, 1960. 2. McCarthy, C. G., Hirsch, H. A., and Finland, M.: Serum Levels after Single Oral Doses of 6-(α-phenoxypropionamido) Penicillanate and Penicillin V, Proc. Soc. Exper. Biol. & Med., *103*:177, 1960. 3. Griffith, R. S.: Comparison of Antibiotic Activity in Sera after the Administration of Three Different Penicillins, Antibiotic Med. & Clin. Therapy, *7*:129, 1960. 4. Editorial: New England J. Med., *263*: 361, 1960. 5. Editorial: New York J. Med., *60*:498, 1960.

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Feb. 1961 (P-487)